LIPPINCOTT MANUAL®

The Washington Manual® of Critical Care

FOURTH EDITION

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THE WASHINGTON MANUAL® OF CRITICAL CARE

Fourth Edition

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SECTION I MANAGEMENT OF SHOCK

1 Introduction to Shock

Marin H. Kollef

Shock is a common problem in the intensive care unit, requiring immediate diagnosis and treatment. It is usually defined by a combination of hemodynamic parameters (mean blood pressure <60 mm Hg, systolic blood pressure <90 mm Hg), clinical findings (altered mentation, decreased urine output), and abnormal laboratory values (elevated serum lactate, metabolic acidosis). The first step is to identify the cause of shock, as each condition will require different interventions. The overall goal of therapy is to reverse tissue hypoperfusion as quickly as possible in order to preserve organ function. Table 1.1 and Algorithms 1.1 and 1.2 offer an introductory approach for determining the main cause of shock. Specific management of the various shock states is presented in the following chapters including the importance of point-of-care ultrasound (POCUS) for the initial evaluation of shock. Early evaluation of shock with POCUS or right heart catheterization will allow determination of the cause of shock and will assist in management.

TABLE 1.1 Hemodynamic and POCUS Patterns Associated With Specific Shock States

Type of Shock	CI	SVR	PVR	S_{VO_2}	RAP	RVP	PAP	PAOP	Cardiac Function	Intravascular Volume
Cardiogenic (eg, myocardial infarction or cardiac tamponade)	↓	↑	N	↓	↑	↑	↑	↑	Poor contractility	Large, noncollapsing IVC
Hypovolemic (eg, hemorrhage, intravascular volume depletion)	↓	↑	N	↓	↓	↓	↓	↓	Hyperdynamic heart	Small, collapsing IVC
Distributive shock (eg, septic, anaphylaxis)	N-↑	↓	N	N-↑	N-↓	N-↓	N-↓	N-↓	Hyperdynamic heart (poor contractility in late phase)	Normal, collapsing IVC
Obstructive (eg, pulmonary embolism)	↓	N-↑	↑	N-↓	↑	↑	↑	N-↓	RV strain and/or poor RV contractility	Large, noncollapsing IVC

↑, increased; ↓, decreased; CI, cardiac index; IVC, inferior vena cava; N, normal; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; POCUS, point-of-care ultrasound; PVR, pulmonary vascular resistance; RAP, right arterial pressure; RVP, right ventricular pressure; S_{VO_2}, mixed venous oxygen saturation; SVR, systemic vascular resistance.

Equalization of RAP, PAOP, diastolic PAP, and diastolic RVP indicates cardiac tamponade.

ALGORITHM 1.1 Main Causes of Shock

ABBREVIATIONS

SBP: systolic blood pressure
MAP: mean arterial pressure
CI: cardiac index

Clinical Picture of Shock
SBP <90 mm Hg
MAP <65 mm Hg
Lactate ≥4 mmol/L

Reduced Cardiac Output
CI <2.2 L/min/m^2
measured by thermodilution method or aortic waveform assessment with transthoracic or esophageal Doppler

Yes

No

Cardiogenic shock

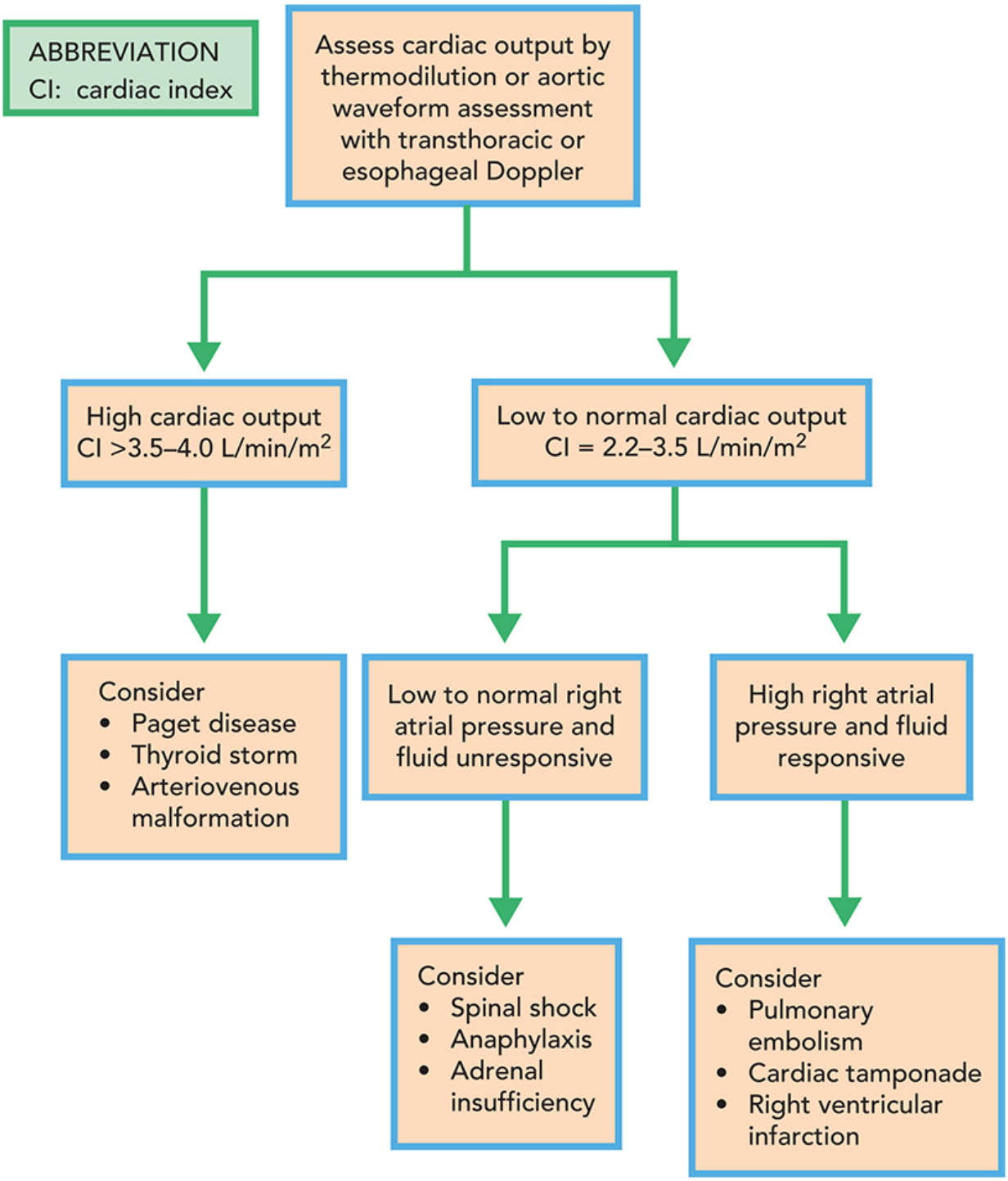
Hypovolemic shock

Septic shock

	Cardiogenic shock	Hypovolemic shock	Septic shock
Pulse pressure	↓	↓	↑
Diastolic pressure	↓	↓	↓↓↓
Extremities	Cool	Cool	Warm/cool
Nailbed blood return	Slow	Slow	Rapid
Jugular venous pressure	↑	↓	↓
Respiratory crepitations	+++	–	–
S_3, S_4 gallop rhythm	+++	–	–
Chest radiograph	Large heart, pulmonary	Diminished cardiac size	Normal, unless pneumonia

	edema		present
Identified site of infection	–	–	+++
Echocardiography	Diminished contractility and ejection fraction	Ventricular chamber obliteration	Hyperdynamic function

ALGORITHM 1.2 **Miscellaneous Causes of Shock**


ABBREVIATION
CI: cardiac index
Assess cardiac output by thermodilution or aortic waveform assessment with transthoracic or esophageal Doppler
High cardiac output
CI >3.5–4.0 L/min/m2
Low to normal cardiac output
CI = 2.2–3.5 L/min/m2
Consider
• Paget disease
• Thyroid storm
• Arteriovenous malformation
Low to normal right atrial pressure and fluid unresponsive
High right atrial pressure and fluid responsive
Consider
• Spinal shock
• Anaphylaxis
• Adrenal insufficiency
Consider
• Pulmonary embolism
• Cardiac tamponade
• Right ventricular infarction

2 Hypovolemic Shock

Benjamin N. Barmaan

Hypovolemic shock occurs from either hemorrhagic or nonhemorrhagic causes. Blood loss from acute hemorrhage results in decreased circulating intravascular volume and can lead to hypoperfusion and inadequate oxygen delivery. If not recognized and treated early, it can lead to significant morbidity and mortality. Common causes include blunt or penetrating trauma, aortic aneurysm rupture, gastrointestinal bleeding, perioperative bleeding, and maternal complications. Table 2.1 provides a classification of hemorrhagic shock based on the percent of whole blood volume lost. In general, the greater the loss of whole blood, the greater the resultant risk of mortality. However, it is important to note that other factors can influence the outcome of hypovolemic shock including age, underlying comorbidities (eg, cardiovascular disease), and the rapidity and adequacy of the volume resuscitation.

TABLE 2.1 Classification of Hypovolemic Shock

Class	Whole Blood Volume Loss (%)	Physical Exam Findings
Class I	<15	Anxiety, normal-appearing vitals
Class II	15-30	Tachycardia, narrowed pulse pressure
Class III	30-40	Tachycardia, decreased and narrowed blood pressure, tachypnea, confusion

Class	Whole Blood Volume Loss (%)	Physical Exam Findings
Class IV	>40	Tachycardia, decreased and narrowed blood pressure, tachypnea, lethargy

Lactic acidosis occurs during hypovolemic shock because of inadequate tissue perfusion. The magnitude of the serum lactate elevation is correlated with mortality in hypovolemic shock and may be an early indicator of tissue hypoperfusion, despite near normal–appearing vital signs. The treatment of lactic acidosis depends on reversing organ hypoperfusion. This is reflected in the equation for tissue oxygen delivery shown further. Optimizing oxygen delivery to tissues requires a sufficient hemoglobin concentration to carry oxygen to tissues. Additionally, ventricular preload is an important determinant of cardiac output. Providing adequate intravascular volume will ensure that stroke volume and cardiac output are optimized to meet tissue demands for oxygen and other nutrients. If, despite adequate preload, cardiac output is not sufficient for the demands of tissues, then vasopressors and/or inotropes can be employed to further increase cardiac output and oxygen delivery.

$$\dot{D}o_2 = Cao_2 \times CO$$
$$Cao_2 = (Hb \times 1.34 \times Sao_2) + 0.0031\ Pao_2$$
$$CO = SV \times HR$$

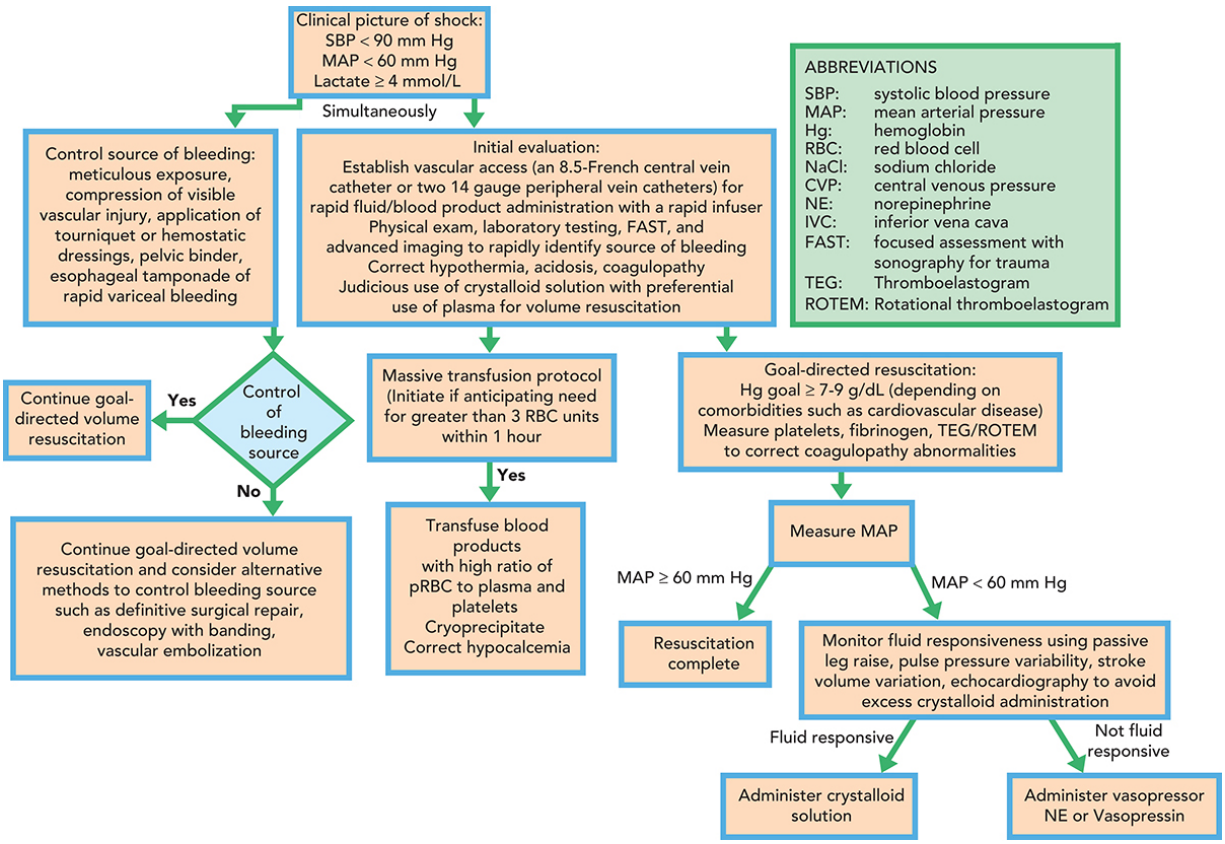
where $\dot{D}o_2$ is oxygen delivery, Cao_2 arterial oxygen content, Co cardiac output, Hb hemoglobin concentration, Sao_2 arterial hemoglobin oxygen saturation, Pao_2 arterial oxygen tension, SV stroke volume, and HR heart rate.

The treatment goals in hypovolemic shock are to control the source of hemorrhage and to administer adequate intravascular volume replacement. Control of the source of hemorrhage may be as simple as placing a pressure dressing on an open bleeding wound,

or it may require urgent operative exploration to identify and control the bleeding source from an intra-abdominal or intrathoracic injury. Angiographic embolization of a bleeding vessel may also be helpful for bleeding injuries that are not amenable to surgical intervention (eg, multiple pelvic fractures with ongoing hemorrhage). Therefore, most episodes of hypovolemic shock are managed by trauma specialists, usually in the emergency department setting. However, all clinicians caring for critically ill patients should be able to recognize the early clinical manifestations of hypovolemic shock and to initiate appropriate resuscitation.

The steps for the fluid management of hypovolemic shock is provided in Algorithm 2.1. At least two large-bore (14-16 gauge or larger) peripheral vein catheters and/or an 8.5-French central vein catheter should be placed to allow rapid blood product and crystalloid administration to restore the patient's intravascular volume while simultaneously trying to identify and treat the source of bleeding. A mechanical rapid transfusion device should also be used to decrease the time required for each unit of blood or liter of crystalloid to be infused. A fluid warmer should be used in order to prevent worsening hypothermia. In a patient with ongoing hemorrhage, group O blood should be given. Most hospitals will employ 4 units of Rh-positive O blood for men and women who are not in childbearing age and Rh-negative O blood for women who are in childbearing age. Type-specific blood is usually administered after the first 4 units of nontyped blood are given. The goal of blood transfusion therapy during ongoing hemorrhage is to maintain the hemoglobin value in the range of 7 to 9 g/dL depending on comorbidities such as cardiovascular disease or other signs of end-organ hypoperfusion.

ALGORITHM 2.1 **Management of Hypovolemic Shock**


Clinical picture of shock:
SBP < 90 mm Hg
MAP < 60 mm Hg
Lactate ≥ 4 mmol/L
Simultaneously
Control source of bleeding: meticulous exposure, compression of visible vascular injury, application of tourniquet or hemostatic dressings, pelvic binder, esophageal tamponade of rapid variceal bleeding
Initial evaluation:
Establish vascular access (an 8.5-French central vein catheter or two 14 gauge peripheral vein catheters) for rapid fluid/blood product administration with a rapid infuser
Physical exam, laboratory testing, FAST, and advanced imaging to rapidly identify source of bleeding
Correct hypothermia, acidosis, coagulopathy
Judicious use of crystalloid solution with preferential use of plasma for volume resuscitation
ABBREVIATIONS
SBP: systolic blood pressure
MAP: mean arterial pressure
Hg: hemoglobin
RBC: red blood cell
NaCl: sodium chloride
CVP: central venous pressure
NE: norepinephrine
IVC: inferior vena cava
FAST: focused assessment with sonography for trauma
TEG: Thromboelastogram
ROTEM: Rotational thromboelastogram
Control of bleeding source
Yes
Continue goal-directed volume resuscitation
No
Continue goal-directed volume resuscitation and consider alternative methods to control bleeding source such as definitive surgical repair, endoscopy with banding, vascular embolization
Massive transfusion protocol (Initiate if anticipating need for greater than 3 RBC units within 1 hour
Yes
Transfuse blood products with high ratio of pRBC to plasma and platelets
Cryoprecipitate
Correct hypocalcemia
Goal-directed resuscitation:
Hg goal ≥ 7-9 g/dL (depending on comorbidities such as cardiovascular disease)
Measure platelets, fibrinogen, TEG/ROTEM to correct coagulopathy abnormalities
Measure MAP
MAP ≥ 60 mm Hg
Resuscitation complete
MAP < 60 mm Hg
Monitor fluid responsiveness using passive leg raise, pulse pressure variability, stroke volume variation, echocardiography to avoid excess crystalloid administration
Fluid responsive
Administer crystalloid solution
Not fluid responsive
Administer vasopressor NE or Vasopressin

In addition to the initial administration of crystalloid and red blood cells, other therapies will be required in patients with hypovolemic shock. These are summarized in Table 2.2 and are especially important for patients requiring massive transfusions or those with ongoing blood loss. There should be an early consideration and rapid initiation of a massive transfusion protocol if the patient may require more than 3 units of red blood cells within 1 hour as early activation has been shown to improve outcomes. The loss of intravascular volume and blood components leads to the lethal triad of hemorrhage: acidosis, hypothermia, and coagulopathy. The principles of damage control resuscitation should be implemented to correct the lethal triad with warming techniques to correct hypothermia, judicious use of crystalloids to avoid hemodilution coagulopathy, and higher ratios of plasma and platelet transfusions to red blood cells. There should be a preference to resuscitate patients with plasma as this has been shown to repair the damaged endothelial glycocalyx. Large-volume administration of fluids is

associated with worse outcomes such as respiratory failure and compartment syndromes and should, therefore, be avoided when possible. Dynamic markers of volume responsiveness such as pulse pressure variation and volume assessment with echocardiography can be helpful to guide volume administration. When massive transfusion protocol has been discontinued, goal-directed correction of coagulopathy should be guided with the use of viscoelastic hemostatic assay such as thromboelastogram (TEG) and standard coagulation panels.

TABLE 2.2 Adjunctive Therapies for Hypovolemic Shock

Therapy	Rationale
Airway control	To provide appropriate gas exchange in the lungs and to prevent aspiration
Cardiac/hemodynamic monitoring	To identify dysrhythmias and inadequate fluid resuscitation (Algorithm 2.1)
Platelet/fresh frozen plasma/cryoprecipitate administration	Required because of dilutional effects of crystalloid and blood administration as well as consumption from ongoing bleeding The prothrombin time and partial thromboplastin time should be corrected and the platelet count should be kept >50,000/mm^3 with ongoing bleeding.
Activated factor VII, antifibrinolyic agents (tranexamic acid)	Should be considered in the presence of diffuse or nonoperative ongoing hemorrhage when clotting abnormalities have been corrected
Reversal of anticoagulation	Consider administering prothrombin complex concentrate, fresh frozen plasma, Andexanet alfa, or idarucizumab for patients on anticoagulation therapy

Therapy	Rationale
ROTEM and TEG	Point-of-care tests that can rapidly assess the clot kinetics to assist with goal-directed correction of coagulopathy
Calcium chloride, magnesium chloride	To reverse ionized hypocalcemia and hypomagnesemia resulting from the administration of citrate with transfused blood, which binds ionized calcium and magnesium
Rewarming techniques (eg, warm fluids, blankets, radiant lamps, head covers, warmed humidified air, heated body cavity lavage)	Hypothermia is a common consequence of massive blood transfusion that can contribute to cardiac dysfunction and coagulation abnormalities.
Monitor for and treat for transfusion-related complications including transfusion-related acute lung injury (TRALI) and transfusion reactions	These are immunologically mediated, requiring appropriate use of mechanical ventilation with positive end-expiratory pressure for TRALI and bronchodilators and corticosteroids for severe bronchoconstriction, subglottic edema, and anaphylaxis.
Extracorporeal membrane oxygenation (ECMO)	To allow for lung-protective ventilation and/or support severe refractory hypoxia in patients with acute respiratory distress syndrome (ARDS) from massive blood transfusions
Resuscitative endovascular balloon occlusion of the aorta (REBOA)	Selective endovascular occlusion of the aorta as a temporizing measure to preferentially perfuse the brain and heart until definitive hemostasis is achieved
Antibiotics	When open dirty or contaminated wounds are present, antibiotics are used to prevent and treat bacterial infections.
Corticosteroids	For patients presumed to have adrenal injury and patients unable to mount an appropriate stress response

ROTEM, rotational thromboelastometry; TEG, thromboelastogram.

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3 Sepsis and Septic Shock

Brendan J. Kurtz and Marin H. Kollef

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. In the United States, approximately 750,000 cases of sepsis occur each year. The mortality associated with sepsis ranges from 30% to 50%, with mortality increasing with advancing age. Although complex, the pathophysiology of sepsis involves a series of interacting pathways involving immune stimulation, immune suppression, hypercoagulation, and hypofibrinolysis. Cardiovascular management plays an important role in the treatment of sepsis and septic shock. Hypotension occurs because of failure of vasoconstriction by vascular smooth muscle, resulting in peripheral vasodilation. Cardiovascular resuscitation has been demonstrated to be an important determinant of survival in patients with septic shock. In addition to cardiovascular management, appropriate initial antimicrobial treatment of patients with sepsis also appears to be an important determinant of patient outcome. Table 3.1 provides the new consensus definitions for sepsis and septic shock.

TABLE 3.1 Consensus Definition of Sepsis

Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Organ dysfunction	Increase in the Sequential Organ Failure Assessment (SOFA) score ≥2
Septic shock	Vasopressors to maintain a mean arterial pressure ≥65 mm Hg and lactate >2 mmol/L in the absence of hypovolemia
Poor	Quick SOFA

outcomes for sepsis *(at least two of the following)*	• Respiratory rate ≥22/min • Altered mentation • Systolic blood pressure ≤100

The unscrambling of the complex pathophysiology associated with sepsis and septic shock has made much progress. Unfortunately, no proven agent targeting the pathways involved in septic shock is currently available. Table 3.2 highlights the supportive medications most commonly used in septic shock. The challenge for clinicians is the integration of these pharmacotherapies to confer the recognized survival benefit into critical care practice. The Surviving Sepsis Campaign has teamed with the Institute for Healthcare Improvement to create the Sepsis Bundles, which are designed in an effort to optimize the timing, sequence, and goals of the individual elements of care as delineated in the Surviving Sepsis Guidelines. The benefits associated with the use of comprehensive treatment protocols integrating goal-directed hemodynamic stabilization, early appropriate antimicrobial therapy, and associated adjunctive sepsis therapies initiated in the emergency department and continued in the intensive care unit (ICU) have been reported in several earlier prospective trials (Algorithms 3.1 and 3.2). However, more recent trials evaluating goal-directed therapy in septic shock have shown no benefit compared to current standard practice, which includes administering intravenous antibiotics and adequate fluid resuscitation as determined by the bedside clinician.

TABLE 3.2 Medications Commonly Used in Septic Shock

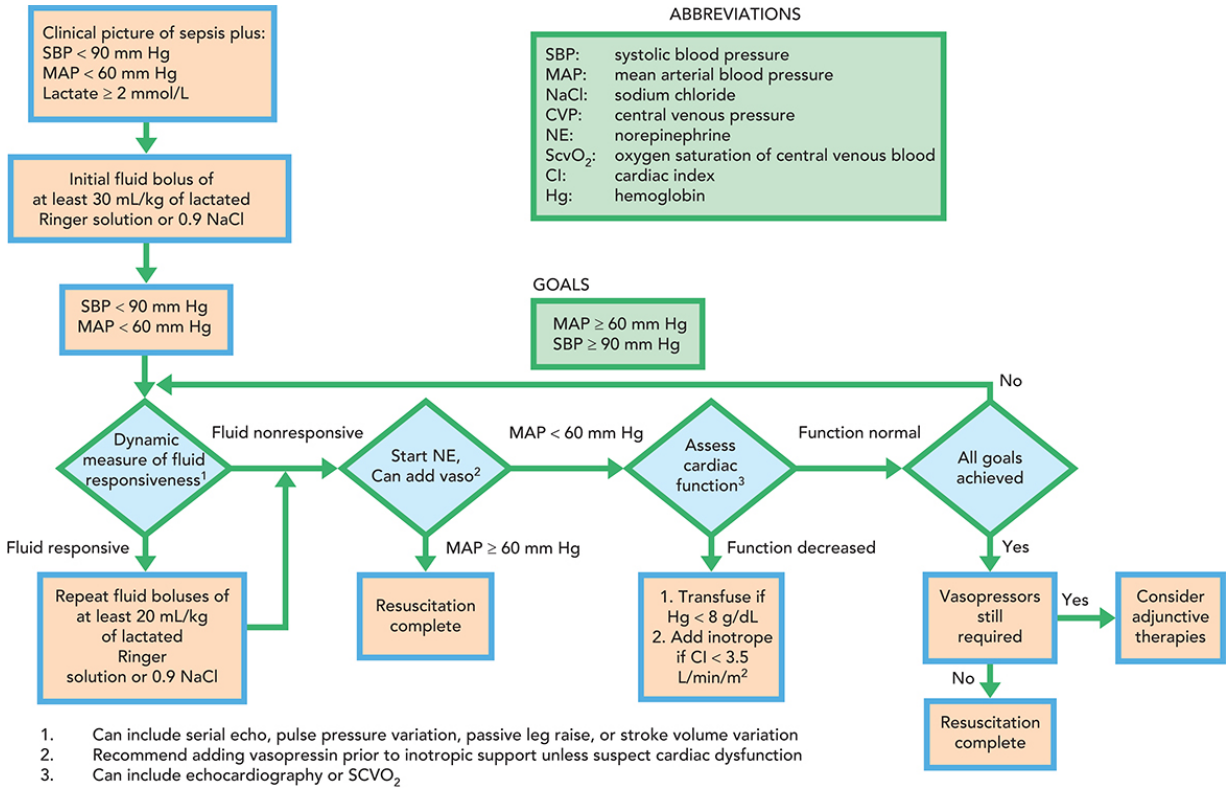
		CO	MAP	SVR
I. Vasopressors				
Norepinephrine	0.05-0.5 mcg/kg/min	−/+	++	+++

		CO	MAP	SVR
Dopamine	5-20 mcg/kg/min	++	+	++
Epinephrine	0.05-2 mcg/kg/min	++	++	+++
Phenylephrine	2-10 mcg/kg/min	0	++	+++
Vasopressin	0.04 units/min	0	+++	+++
II. Inotrope				
Dobutamine	2.5-10 mcg/kg/min	+++	−/+	−/0
III. Corticosteroids[a]				
Hydrocortisone (+/− fludrocortisone 50 mcg daily)	50 mg every 6 h			
IV. Antibiotic management (see Algorithm 3.2)				

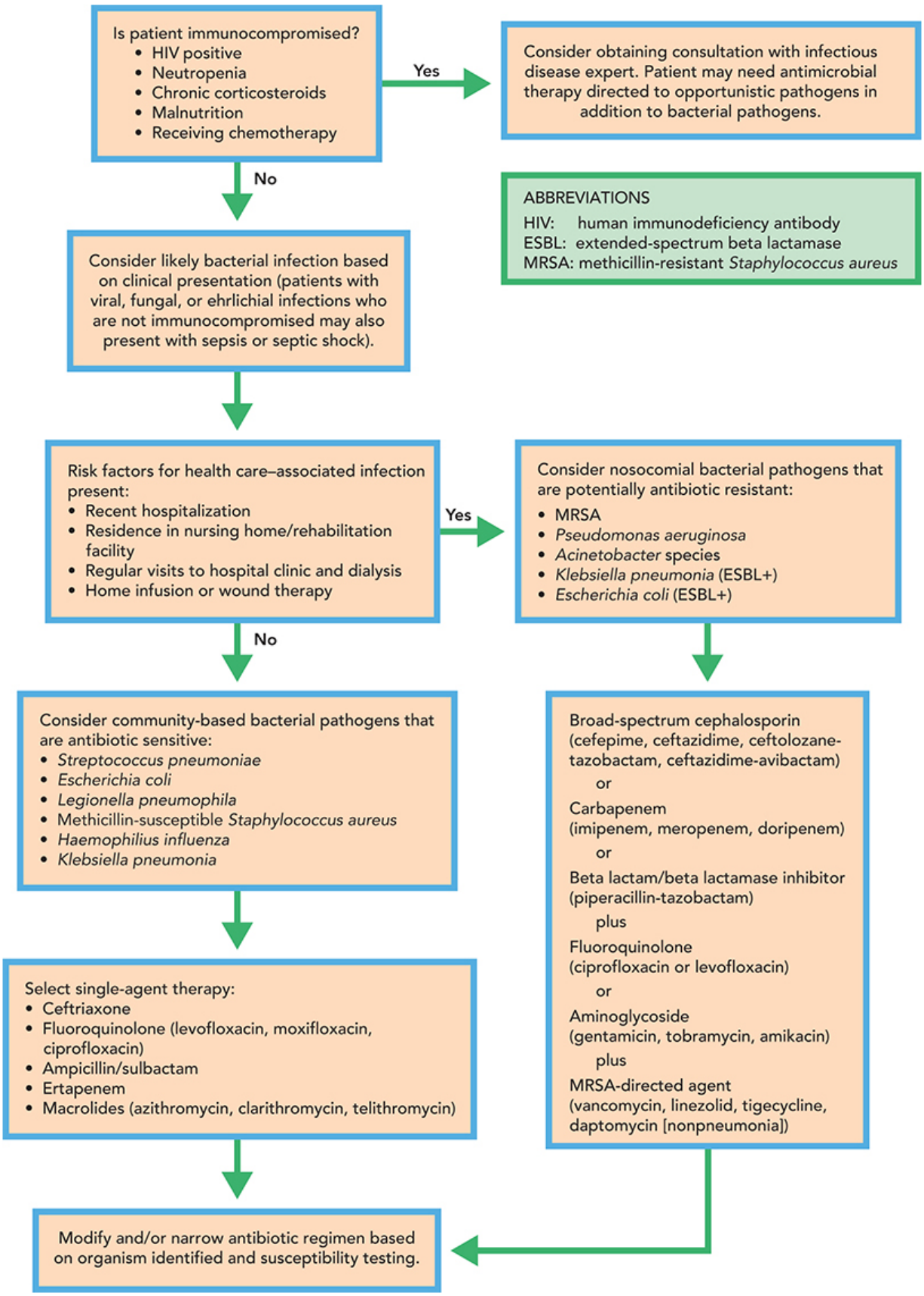
[a]The benefits of corticosteroids in septic shock are limited to patients with vasopressor-dependent septic shock despite adequate fluid resuscitation.

CO, cardiac output; MAP, mean arterial blood pressure; SVR, systemic vascular resistance.

ALGORITHM 3.1 Fluid Management of Septic Shock


Clinical picture of sepsis plus:
SBP < 90 mm Hg
MAP < 60 mm Hg
Lactate ≥ 2 mmol/L
Initial fluid bolus of at least 30 mL/kg of lactated Ringer solution or 0.9 NaCl
SBP < 90 mm Hg
MAP < 60 mm Hg
ABBREVIATIONS
SBP: systolic blood pressure
MAP: mean arterial blood pressure
NaCl: sodium chloride
CVP: central venous pressure
NE: norepinephrine
ScvO2: oxygen saturation of central venous blood
CI: cardiac index
Hg: hemoglobin
GOALS
MAP ≥ 60 mm Hg
SBP ≥ 90 mm Hg
No
Dynamic measure of fluid responsiveness1
Fluid nonresponsive
Start NE, Can add vaso2
MAP < 60 mm Hg
Assess cardiac function3
Function normal
All goals achieved
Fluid responsive
Repeat fluid boluses of at least 20 mL/kg of lactated Ringer solution or 0.9 NaCl
MAP ≥ 60 mm Hg
Resuscitation complete
Function decreased
1. Transfuse if Hg < 8 g/dL
2. Add inotrope if CI < 3.5 L/min/m2
Yes
Vasopressors still required
Yes
Consider adjunctive therapies
No
Resuscitation complete
1. Can include serial echo, pulse pressure variation, passive leg raise, or stroke volume variation
2. Recommend adding vasopressin prior to inotropic support unless suspect cardiac dysfunction
3. Can include echocardiography or SCVO2

ALGORITHM 3.2 Antibiotic Management of Sepsis and Septic Shock


Is patient immunocompromised?
• HIV positive
• Neutropenia
• Chronic corticosteroids
• Malnutrition
• Receiving chemotherapy
Yes
Consider obtaining consultation with infectious disease expert. Patient may need antimicrobial therapy directed to opportunistic pathogens in addition to bacterial pathogens.
No
ABBREVIATIONS
HIV: human immunodeficiency antibody
ESBL: extended-spectrum beta lactamase
MRSA: methicillin-resistant Staphylococcus aureus
Consider likely bacterial infection based on clinical presentation (patients with viral, fungal, or ehrlichial infections who are not immunocompromised may also present with sepsis or septic shock).
Risk factors for health care–associated infection present:
• Recent hospitalization
• Residence in nursing home/rehabilitation facility
• Regular visits to hospital clinic and dialysis
• Home infusion or wound therapy
Yes
Consider nosocomial bacterial pathogens that are potentially antibiotic resistant:
• MRSA
• Pseudomonas aeruginosa
• Acinetobacter species
• Klebsiella pneumonia (ESBL+)
• Escherichia coli (ESBL+)
No
Consider community-based bacterial pathogens that are antibiotic sensitive:
• Streptococcus pneumoniae
• Escherichia coli
• Legionella pneumophila
• Methicillin-susceptible Staphylococcus aureus
• Haemophilius influenza
• Klebsiella pneumonia
Broad-spectrum cephalosporin (cefepime, ceftazidime, ceftolozane-tazobactam, ceftazidime-avibactam)
or
Carbapenem (imipenem, meropenem, doripenem)
or
Beta lactam/beta lactamase inhibitor (piperacillin-tazobactam)
plus
Fluoroquinolone (ciprofloxacin or levofloxacin)
or
Aminoglycoside (gentamicin, tobramycin, amikacin)
plus
MRSA-directed agent (vancomycin, linezolid, tigecycline, daptomycin [nonpneumonia])
Select single-agent therapy:
• Ceftriaxone
• Fluoroquinolone (levofloxacin, moxifloxacin, ciprofloxacin)
• Ampicillin/sulbactam
• Ertapenem
• Macrolides (azithromycin, clarithromycin, telithromycin)
Modify and/or narrow antibiotic regimen based on organism identified and susceptibility testing.

The significance of early, aggressive volume resuscitation and hemodynamic stabilization was initially demonstrated in a randomized, controlled, single-center trial in patients who presented to the emergency department with signs of septic shock, as published by Rivers et al. Administration of crystalloids, red blood cell transfusions, vasopressors, and inotropes based on aggressive monitoring of intravascular volume and a tissue oxygen marker within 6 hours of presentation to the emergency department resulted in a 16% decrease in absolute 28-day mortality. The major differences in treatment between the intervention and control groups were in the volume of intravenous fluids received, the number of patients transfused packed red blood cells, the use of dobutamine, and the presence of a dedicated study team for the first 6 hours of care.

The implementation of treatment pathways mimicking the interventions of the well-scripted, carefully performed procedures employed by Rivers et al has been put into practice in the clinical setting. Micek et al employed standardized order sets that focused on intravenous fluid administration and the appropriateness of initial antimicrobial therapy for sepsis and septic shock. Patients managed in this manner were more likely to receive intravenous fluids >20 mL/kg of body weight prior to vasopressor administration, and consequently were less likely to require vasopressor administration at the time of transfer to the ICU. Patients managed with this approach were also more likely to be treated with an appropriate initial antimicrobial regimen. As a result of the aggressive management initiated in the emergency department and continued in the ICU, patients managed via the sepsis order sets had statistically shorter hospital lengths of stay and a lower risk for 28-day mortality. Similar results have been reported from a multicenter study coordinated by the Surviving Sepsis Campaign Group and supported by a recently performed meta-analysis.

It is important to note that not all studies have shown benefit when using early goal-directed therapy in the treatment of sepsis or septic shock. Notably, the ProMISe, ARISE, and ProCESS trials all failed to show that goal-directed protocolized resuscitation of septic shock

improved outcome. It is important to recognize that the patients in these three trials were not as ill as those in the original Rivers trial as manifested by lower mortality in the control arms (29%, 19%, 19%, respectively, vs 46% in the Rivers trial) and higher central venous oxygen saturation (ProMISe 74%, ARISE 76% vs Rivers 49%). As a result, these trials do not necessarily exclude a survival benefit of early goal-directed resuscitation in patients with septic shock; however, the results do call into question the perceived benefits of early goal-directed protocols in the treatment of sepsis. When Andrews and colleagues performed their randomized controlled trial looking at 6-hour goal-directed therapy versus usual care, they found that patients in the protocolized care group had a 15% higher mortality as well as were more likely to have signs of harm from fluid overload.

Additionally, while early studies showed a temporal benefit using early initiation of goal-directed therapy in patients with sepsis, the methods and potential bias of these studies have since been called into question. For example, while Seymour et al showed that each additional hour needed to complete the 3-hour sepsis bundle increased mortality, critics have argued that patients were not randomized into groups that received care at various time thresholds, the retrospective analytic design of the trials introduces methodological flaws, and the effect size was minimal and driven only by the sickest patients in the study. In fact, the only prospective, randomized clinical trial evaluating the use of early antibiotic administration, the PHANTASi trial by Alam et al, failed to show any benefit in 28-day mortality, 90-day mortality, rate of ICU admission, or length of ICU or hospital stay. It should be noted that only 4% of patients in this study had septic shock, limiting its extrapolation to the sickest subset of septic shock patients.

The use of lactate reduction to drive therapy has also been called into question. The ANDROMEDA-SHOCK trial randomized patients into a lactate-driven fluid resuscitation protocol compared to a capillary refill time–driven protocol. The patients in the lactate-driven protocol were noted to have a higher 28-day mortality.

Due to perceived low quality of evidence cited in the Surviving Sepsis Campaign Guidelines, multiple professional organizations have released their own clinical guidelines regarding the management of sepsis and septic shock including the Infectious Disease Society of America (IDSA) and the American College of Emergency Physicians (ACEP). Notably, the ACEP guidelines do not recommend a 30 mL/kg intravenous fluid bolus, preferring individualized fluid resuscitation as determined appropriate by the bedside clinician. Additionally, they recommend against the use of lactate reduction to guide ongoing fluid resuscitation given the multifactorial cause of elevated lactate in patients with sepsis. The IDSA argues that SIRS criteria should not be used in the identification of septic shock given its poor specificity and instead recommends that only suspicion of infection and signs of shock should be used.

In 2021, the Surviving Sepsis Campaign downgraded its guidance for a 30 mL/kg fluid bolus in the initial resuscitation of patients with sepsis-induced hypoperfusion or septic shock from a strong recommendation to a weak recommendation. Additionally, they now only recommend using balanced crystalloids and recommend against the use of normal saline, citing the 2018 SMART clinical trial. They also now suggest using capillary refill time in addition to serum lactate to guide resuscitation. Finally, they recommend using dynamic measures to guide fluid resuscitation after the initial fluid bolus, such as pulse pressure variation, stroke volume variation, or echocardiography findings in response to passive leg raise or fluid bolus. It should be noted that since the release of the 2021 Surviving Sepsis Campaign Guidelines, the IDSA has since changed its position and now endorses these guidelines.

In summary, the initial management of patients with septic shock appears to be critical in terms of determining outcome. Institution of standardized physician order sets, or some other systematic timely approach, for the management of patients with severe infections appears to consistently improve the delivery of therapies and may improve patient outcomes. While there are some associated risks with these treatment pathways, their implementation has become the

standard of care for the management of septic shock. Moreover, emerging clinical experience suggests that achievement of negative fluid balance after the initial resuscitation phase, and stabilization of the patient with septic shock, confers additional survival benefit.

SUGGESTED READINGS

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4 Cardiogenic Shock

Adam N. Lick, Adam M. May, and Joel D. Schilling

Cardiogenic shock (CS) is a state of end-organ hypoperfusion and tissue hypoxia due to reduced cardiac output (CO) despite adequate intracardiac filling pressures. If this condition persists, the failure of oxygen delivery to meet the metabolic demands of the body will ultimately culminate into multisystem organ dysfunction and patient death.

In clinical practice, CS can be identified using either clinical criteria or invasive hemodynamic data. The criteria used to define CS in clinical trials are summarized in Table 4.1. While trial criteria and definitions may be useful in identifying CS, many CS patients fall outside of these parameters. For instance, patients with CS can present with a systolic blood pressure (BP) >90 mm Hg yet still have evidence of end-organ hypoperfusion and tissue hypoxia.

TABLE 4.1 Pooled Trial Definitions of Cardiogenic Shock

- Systolic BP <90 mm Hg for ≥30 min or supportive interventions to maintain >90 mm Hg.
- Evidence of end-organ damage
  - Clinical: cold extremities, narrow pulse pressure, encephalopathy, oliguria
  - Laboratory: metabolic acidosis, elevated serum lactate, elevated creatinine, elevated liver enzymes
- Hemodynamic data: CI <2.2 L/min/m^2, PCWP >15 mm Hg

BP, blood pressure; CI, cardiac index; PCWP, pulmonary capillary wedge pressure.

Despite the recent advances in coronary revascularization and temporary mechanical circulatory support (MCS) devices, CS remains a leading cause of morbidity and mortality among patients with cardiovascular disease. The mortality rate from CS remains exceptionally high, with rates typically exceeding 40% in contemporary registries and clinical trials. In addition, CS is associated with longer hospital stays and greater health care costs. Furthermore, CS survivors report reduced quality of life, impaired mobility, and other psychosocial consequences after recovery.

Etiology

A wide variety of cardiovascular disease pathologies and insults can lead to CS (Table 4.2). One of the more common causes of CS is acute myocardial infarction (AMI). An estimated 5% to 12% of AMI cases are complicated by CS, with advanced age and late presentation being significant risk factors. In this setting, CS typically occurs when >40% of the myocardium is damaged or in the setting of a mechanical complication (eg, ventricular septal defect [VSD], free wall rupture, papillary muscle rupture). However, smaller ischemic insults may provoke CS in patients with preexisting left ventricular (LV) dysfunction. Over the last couple of decades, the incidence of CS due to AMI has steadily declined because of early percutaneous coronary intervention (PCI). An analysis of the US National Inpatient Sample disclosed that the incidence of CS due to AMI had decreased from 39.2% to 28.5% between 2004 and 2018.

TABLE 4.2 Common Etiologies of Cardiogenic Shock

Left Ventricular Failure
Large territory AMI
Mechanical complications of AMI (eg, papillary muscle rupture)
Small territory AMI with preexisting ventricular dysfunction
Demand ischemia in setting of preexisting cardiomyopathy
Fulminant myocarditis (infectious or toxin/drug)
Stress-induced cardiomyopathy (Takotsubo or apical ballooning)
Acute transplant rejection
Peripartum cardiomyopathy
Post-cardiotomy
Myocardial contusion
Myocardial stunning after cardiac arrest
Acute-on-chronic progression of left ventricular systolic dysfunction
Right Ventricular Failure
Acute right ventricular myocardial infarction
Fulminant myocarditis (infectious, toxin/drug)
Acute transplant rejection
Post-cardiotomy
Myocardial contusion
Myocardial stunning after cardiac arrest
Acute-on-chronic progression of existing right ventricular systolic dysfunction
Progressive RV failure after implantation of LVAD

Miscellaneous
Cardiac arrhythmias (eg, third-degree heart block or ventricular tachycardia)
Acute or progressive valvular heart disease
Prosthetic valve thrombosis
Hypertrophic obstructive cardiomyopathy
Left atrial myxoma
Endocrine disorders (eg, Myxedema coma)
Calcium channel or beta-blocker overdose
Anthracyclines
Checkpoint inhibitor myocarditis

AMI, acute myocardial infarction; LVAD, left ventricular assist device; RV, right ventricular.

The combination of improved medical therapies for chronic heart failure (HF), rapid revascularization for AMI, and the use of internal cardiac defibrillators has led to an increase in the number of patients with advanced HF. These patients are at high risk of deterioration and can present with acute-on-chronic decompensated HF with coexisting CS provoked by a wide variety of insults including acute coronary syndromes, infection, arrhythmia, pulmonary embolism, or progression of the underlying cardiomyopathy. At present, about 30% of all presentations of CS have some form of advanced HF, and current trends indicate that a larger proportion of CS patients will continue to increase from patients preexisting HF.

Hemodynamic Profile and Phenotype

CS is a complex, dynamic, and heterogeneous condition that can present with a wide variety of phenotypic patterns: (i) acute de novo CS (eg, after an AMI or myocarditis) versus CS due to acute-on-chronic systolic HF; (ii) LV predominant versus right ventricular (RV) predominant versus biventricular CS; and (iii) mixed shock versus pure CS. Correctly categorizing the CS phenotype helps guide therapeutic interventions and inform prognosis.

CS severity may be classified according to the Society for Cardiovascular Angiography and Interventions (SCAI) 5-tier classification system, introduced in 2019. These stages range from A (“at risk”) with no evidence of hypotension or hypoperfusion to E (“extremis”) with profound hypoperfusion refractory to intervention. Beyond characterizing CS severity, the SCAI classification system enables the identification of patients who are failing to respond to interventions, or those who are deteriorating and should

be considered for more intensive therapy. Additionally, this system has been retrospectively validated and correlates well with both in-hospital and intensive care unit (ICU) mortality. For example, patients with stage E classification have an in-hospital mortality of nearly 70%.

Pathophysiology

Regardless of the underlying etiology, reduced CO leading to systemic hypoperfusion is the hallmark manifestation of CS. This combination of tissue hypoxia with venous congestion can give rise to a downward spiral of maladaptive physiologic responses that promote end-organ dysfunction, ultimately culminating in patient death. For example, compensatory arteriolar vasoconstriction and tachycardia serve to increase mean arterial pressure (MAP) in the setting of reduced CO; however, this response may result in myocardial ischemia due to increased myocardial oxygen consumption demand. This in turn may worsen myocardial performance and CO. In addition, the increase in filling pressures that initially occurs to maintain stroke volume (SV) can further impair coronary perfusion pressure and promote myocardial ischemia, especially in the setting of reduced MAP. The rise in intracardiac pressures can also lead to pulmonary edema, which further exacerbates hypoxemia and tissue ischemia. Additionally, pulmonary edema may also elicit profound pulmonary vasoconstriction and increase pulmonary vascular resistance, which impairs blood flow delivery to the LV and increases demand for the RV. Moreover, reduced MAP may also impair renal perfusion and lead to acute kidney injury and activation of the renin-angiotensin-aldosterone system, both of which will increase sodium retention and heighten the risk of complications due to volume overload. Lastly, simultaneous with hemodynamic perturbations, tissue hypoperfusion may trigger the production of inflammatory mediators and nitric oxide as part of a maladaptive “hemo-metabolic cascade.” This in turn leads to global vasodilation that impairs compensatory arteriolar vasoconstriction and reduces cardiac preloading from high-capacitance venous vessels, which will potentiate reduced CO and MAP, and thereby deepen a vicious and self-perpetuating cycle of end-organ hypoperfusion and inflammation.

Clinical Assessment

Prompt recognition of CS is essential for management, as timely and appropriate treatment can significantly reduce mortality. Figure 4.1 illustrates the initial assessment strategy.

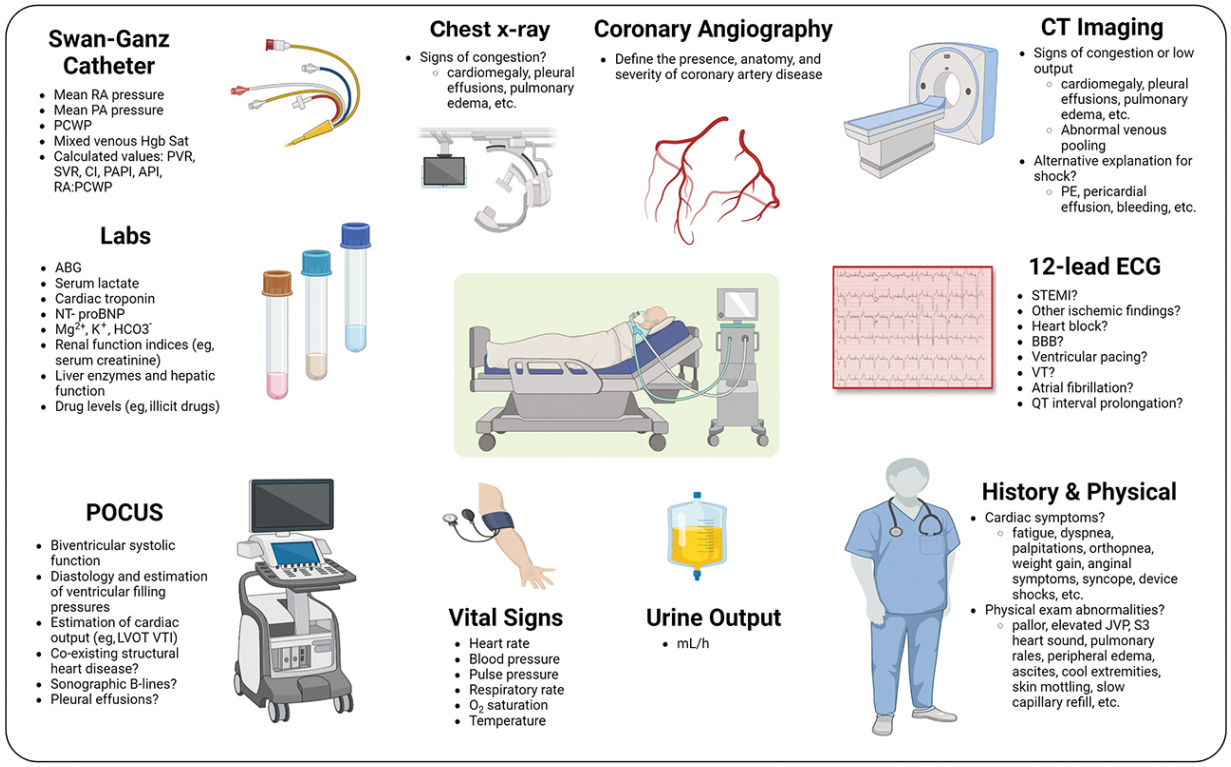

FIGURE 4.1 **Overview of initial clinical and diagnostic evaluation of cardiogenic shock.** ABG, arterial blood gas; API, aortic pulsatility index; BBB, bundle branch block; CI, cardiac index; ECG, electrocardiogram; HCO_3^-, bicarbonate; Hgb, hemoglobin; ICD, implantable cardiac defibrillator; JVP, jugular venous pressure; K^+, potassium; LVAD, left ventricular assist device; LVOT VTI, left ventricular output velocity time integral; Mg^{2+}, magnesium; NT-pro BNP, *N*-terminal pro-B-type natriuretic peptide; O_2, oxygen; PA, pulmonary artery; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PPM, permanent pacemaker; PVR, pulmonary vascular resistance; RA, right atrium; RA:PCWP, right atrial to pulmonary capillary wedge ratio; Sat, saturation; STEMI, ST-elevation myocardial infarction; SVR, systemic vascular resistance; SVT, supraventricular tachycardia; VA, ventricular arrhythmia; VT, ventricular tachycardia. (Created with BioRender.com.)

VITALS AND PHYSICAL EXAM

Basic vital signs including BP, heart rate, oxygen saturation percentage, body temperature, and urine output are essential in the initial evaluation and

continued monitoring of CS patients. As an attempt to preserve CO and MAP, tachycardia may be present to compensate for low SV. A systolic BP <90 mm Hg is highly specific for a cardiac index (CI) <2.3 L/min/m^2 in patients with an underlying cardiomyopathy. A narrow pulse pressure (eg, <20 mm Hg) may manifest in the setting of low SV and increased systemic vascular resistance (SVR). As seen in other forms of shock, urine output may be decreased.

Physical examination may reveal signs of congestion and diminished perfusion. An elevated jugular venous pressure (JVP) is one of the most sensitive and specific markers of intravascular congestion, especially when >12 cm H_2O above the right atrium. Kussmaul sign may be seen in those with dilated RV causing pericardial restraint and is correlated with worse hemodynamics and clinical outcomes. Other signs of congestion include pulmonary crackles and wheezes, peripheral edema, ascites, hepatojugular reflux, and S3 gallop. Markers of end-organ hypoperfusion are less specific of CS but include cool and mottled extremities, delayed capillary refill, weak pulses, and altered mental status. A detailed cardiac examination should also evaluate for the presence of coexisting cardiac disease, including valvular disease or mechanical complications of an acute myocardial infarct (eg, the harsh murmur of an ischemic VSD). It is important to keep in mind that in the setting of low CO and elevated intracardiac pressures, cardiac murmurs (eg, mitral regurgitation) may be diminished or hardly audible.

LABORATORY EVALUATION

Laboratory studies are essential for the evaluation and management of CS and should include a complete blood count, serum electrolytes, blood urea nitrogen (BUN), creatinine, liver enzymes and liver function tests, *N*-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin (Hs-trop), serum lactate, and central venous oxygen saturation ($ScvO_2$). As the $ScvO_2$ is directly related to the concentration of hemoglobin, clinicians should be aware that a low value may be a manifestation of anemia and not necessarily poor CO.

12-LEAD ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) should be obtained on every CS patient. This test is especially important as it may help providers identify acute illnesses responsible for CS, including AMI (eg, ST-segment elevation myocardial infarction) or cardiac dysrhythmias (eg, complete heart block).

IMAGING

Chest x-ray can identify signs of cardiopulmonary congestion, including cardiomegaly, pulmonary edema, pleural effusions, and hilar fullness. Chest computed tomography (CT) can similarly detect cardiopulmonary congestion but may also help entirely exclude alternative etiologies for shock (eg, pulmonary embolism and pericardial effusion).

Coronary angiography is critical for CS patients in the setting of AMI, and early revascularization with PCI should not be delayed. The landmark SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK) trial demonstrated a survival benefit with early revascularization of culprit lesions in patients with CS complicating AMI. Beyond the identification of acute culprit lesions, angiography provides the means to characterize the nature and severity of coronary artery disease that may be contributing to myocardial dysfunction. This is particularly important because obstructive coronary artery disease is a potentially reversible cause of cardiomyopathy to which revascularization may improve patient outcomes.

POINT-OF-CARE ULTRASOUND

Rapid point-of-care echocardiography should be performed as soon as possible to assess biventricular systolic function and to evaluate for other pathology(s) that may be contributing to shock, including valvular heart disease, severe pulmonary hypertension, and AMI-related complications (eg, papillary muscle rupture). It is especially important that clinicians identify structural abnormalities responsible for CS early, as immediate intervention can improve outcomes (eg, cardiac surgery for acute VSD). Bedside echocardiography can also be used to estimate SV (and CO) by measurement of left ventricular outflow tract (LVOT) velocity time integral (VTI). In general, CS patients will have an excessively low LVOT VTI values (eg, <12 cm). If the clinician possesses more advanced echocardiographic skill, a comprehensive assessment of diastolic function may help confirm the presence of elevated intracardiac filling pressures. Furthermore, lung ultrasound can quickly identify the presence of coexisting pleural effusions and cardiogenic pulmonary edema (sonographic B lines).

INVASIVE MONITORING

Arterial catheterization allows for continuous BP monitoring and can be combined with novel monitoring devices that use arterial waveforms to

estimate SV, SV variation, and CO.

Central venous catheters (CVCs) may provide useful information of the patient's underlying hemodynamic state. If placed in the internal jugular or subclavian veins, CVCs can directly measure central venous pressure (CVP) and identify abnormalities in global oxygen delivery and/or consumption (eg, low $ScvO_2$ in CS). Additionally, CVP waveform characteristics can assist in identifying cardiac pathologies responsible for shock (eg, large CV wave in the setting of severe tricuspid regurgitation).

Pulmonary artery catheterization (PAC) with a Swan-Ganz catheter (SGC) can be especially useful in defining the nature and severity of CS. SGCs enable the direct measurement and derivation of a multitude of hemodynamic parameters (Table 4.3) that may provide valuable insights into patients' underlying hemodynamics. Moreover, after SGC placement, the hemodynamic information provided can help clinicians decide upon therapeutic interventions. For example, PAC can help guide the use of vasopressors, inotropic agents, intravenous fluids, diuretics, and device settings for MCS. Additionally, PAC data can be serially monitored to track the clinical course of CS patients, which may be especially helpful for decisions relating to care escalation or deescalation. Furthermore, PAC may also be particularly useful in guiding the treatment of patients with shock states that are both challenging to characterize and manage (eg, mixed cardiogenic and septic shock). Although PAC use has declined in the intensive care setting, new data have highlighted its benefits in the management of CS patients. For example, a 10-year retrospective analysis of registry data from the National Inpatient Sample demonstrated a 9% decrease in mortality with PAC use in CS patients. Similarly, recent observational studies have shown PAC use to have a protective benefit in CS patients, especially more advanced SCAI stage D and E patients.

TABLE 4.3 Swan-Ganz Catheter Hemodynamic Parameters

Parameter	Formula	Normal Range	Clinical Utility
Directly Measured			
Right atrial pressure (RAP)	–	Mean 0-7 mm Hg	Right-sided filling pressures
Right ventricular pressure (RVP)	–	Systolic 15-30 mm Hg Diastolic 1-7 mm Hg	RV performance
Pulmonary artery pressure (PAP)	–	Systolic 15-30 mm Hg Diastolic 4-12 mm Hg Mean 8-20 mm Hg	Used to diagnose and evaluate pulmonary hypertension
Pulmonary capillary wedge pressure (PCWP)	–	Mean 4-12 mm Hg	Left-sided filling pressures
Calculated			
Cardiac output (CO) by Fick By thermodilution	$\frac{\text{Oxygen Consumption}}{\text{Arterial } O_2\text{-Venous } O_2}$ Area under the curve of temperature change over time after injection of 10 mL bolus of cold saline	4-8 L/min	Indicator of LV performance Oxygen delivery Characterize shock Monitor response to therapies
Cardiac index (CI)	$\frac{\text{CO}}{\text{Body Surface Area}}$	2.5-4 L/min/m^2	
Derived			
Systemic vascular resistance (SVR)	$\frac{\text{MAP} - \text{CVP}}{\text{CO}}$	700-1,600 dynes·s/cm^{-5} 8-20 Wood units	Characterize shock Response to therapies
Pulmonary vascular resistance (PVR)	$\frac{\text{Mean PAP} - \text{PCWP}}{\text{CO}}$	100-200 dynes·s/cm^{-5} <2 Wood units	Differentiates pre- vs post- vs combined PH

Pulmonary artery pulsatility index (PAPi)	$\frac{sPAP - dPAP}{RAP}$	>4.8—fewer MAE in cardiovascular population	RV function <3.7—poor outcomes in PH patients <1.0—severe RV failure
Aortic pulsatility index (API)	$\frac{sBP - dBP}{PCWP}$	>2.9—fewer MAE in HF population	<1.45 high mortality in CS
Cardiac power output (CPO)	$\frac{MAP \times CO}{451}$	>1 W	<0.6 high mortality in CS

CS, cardiogenic shock; CVP, central venous pressure; dBP, diastolic blood pressure; dPAP, diastolic pulmonary artery pressure; HF, heart failure; LV, left ventricle; MAE, major adverse events; MAP, mean arterial pressure; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricle; sBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure.

Treatment

TRIAGE AND INITIAL MANAGEMENT

Early identification and rapid intervention are essential for the successful management of CS. Delays in CS recognition, or the institution of stabilizing interventions, contribute to patient mortality and morbidity. CS patients should be triaged or transferred to a level 1 shock center for advanced management options (eg, PCI, MCS devices, and cardiac surgery). Similar to modern care models to rapidly triage patients with occlusive AMI for PCI, a first responder and hospital network system has been proposed for CS with the goal of early triage to a level 1 center. A “Shock Team” consisting of cardiac intensivists, interventional cardiologists, advanced HF specialists, and cardiothoracic surgery provides the expertise to make time-sensitive decisions for care escalation or de-escalation. Several single-center studies in North America have shown a decrease in both in-hospital and 30-day mortality with the use of a Shock Team.

After prompt recognition, CS patients require rapid stabilization with medical therapy, including vasopressors, inotropes, and volume correction. Despite their frequent use for stabilization, there is a lack of high-quality evidence available to guide the initial selection of these therapies. Moreover,

substantial heterogeneity in trial design and patient populations greatly confounds the limited evidence that is available.

In general, vasopressors and inotropes are the foundation to stabilizing patients with CS (Table 4.4). Dobutamine and milrinone are first-line inotropic therapies that work via direct beta-adrenergic stimulation and phosphodiesterase-3 inhibition, respectively. Each produces an increase in CO by enhancing cardiomyocyte contractility and promoting vasodilation. According to current guidelines, inotrope administration has class 1C recommendation for temporizing support; however, inotrope dose and duration should be the lowest possible given their potential for adverse effects, including worsening ischemia and arrhythmia. Milrinone should be used with caution in CS given its longer half-life, potential to worsen hypotension, and the risk of toxic metabolite accumulation that occurs with worsening renal function. Norepinephrine is first-line vasopressor in CS. Norepinephrine is an alpha-agonist with weaker beta-agonist effects; however, it does function as a positive inotropic agent at higher doses. Norepinephrine advantageously increases MAP to salvage end-organ functioning, including the heart via coronary perfusion. Moreover, norepinephrine can increase CO by promoting venous return to a preload responsive heart. Epinephrine is an alpha- and beta-agonist that can also be considered for CS; however, the use of epinephrine has been associated with higher rates of a refractory shock compared to norepinephrine. Dopamine is another agent that has combined inotropic and vasopressor effects. At low infusion rates (ie, 0.5-2 μg/kg/min), dopamine promotes renal perfusion. At intermediate infusion rates (ie, 2-10 μg/kg/min), dopamine stimulates increased myocardial contractility and increased heart rate to increase CO. At higher infusion rates (ie, >10 μg/kg/min), dopamine promotes vasoconstriction and increased BP via increased alpha-agonist activity. Dopamine is associated with an increased risk for tachyarrhythmias, and its use is discouraged because it was associated with a higher mortality rate in a subgroup of CS patients in the Sepsis Occurrence in Acutely Ill Patients (SOAP) II trial. Lastly, combination therapy with an inotrope and vasopressors, such as dobutamine and norepinephrine, may be a particularly effective strategy to simultaneously increase CO and MAP.

TABLE 4.4 Common Medications Used in Cardiogenic Shock

	Action	Dose	Inotropy	Use and Precautions

	Action	Dose	Inotropy	Use and Precautions
Vasopressors				
Norepinephrine	$Alpha_1$ > $beta_1$	0.01-2.0 mcg/kg/min	+	First-tier agent for hypotension in all shock
Epinephrine	$Beta_{1/2}$ > $alpha_1$	0.01-0.3 mcg/kg/min	+++	Second-tier inotrope and vasopressor
Vasopressin	V_{1a}	0.04 units/min	0	Second-line vasopressor Increases water reabsorption in kidneys
Phenylephrine	$Alpha_1$	0.5-4 mcg/kg/min	0	Outflow obstruction (LVOT) Reflex bradycardia
Angiotensin II	AT_1	2.5-40 ng/kg/min	0	Refractory shock
Dopamine	DA/$beta_1$ > $alpha_1$	2.5-20 mcg/kg/min	++	Dose-dependent vasopressor and inotrope Can be arrhythmogenic
Inotropes				
Dobutamine	$Beta_{1/2}$ > $alpha_1$/$beta_2$	2.5-20 mcg/kg/min	+++	First-tier inotrope Can increase myocardial o_2 demand in recent MI
Milrinone	PDE_3 inhibitor	0.1-0.75 mcg/kg/min	+++	First-tier inotrope Renally cleared, monitor closely with renal dysfunction Hypotension
Vasodilators				
Nitroprusside	Vascular smooth muscle	0.3-10 mcg/kg/min	0	Decreases SVR Thiocyanate toxicity with prolonged use and in advanced CKD

AT, angiotensin; CKD, chronic kidney disease; DA, dopamine receptor; LVOT, left ventricular outflow tract; MI, myocardial infarction; NO, nitric oxide; PDE_3, phosphodiesterase 3; SVR, systemic vascular resistance.

Cardiogenic Shock Associated With Acute Myocardial Infarction

Early revascularization reduces mortality in CS patients with an AMI. The SHOCK trial, which compared emergency revascularization to initial medical stabilization for CS patients with AMI, demonstrated that patients <75 years of age had ~20% relative risk reduction in mortality with early revascularization. Notably, 36% of the patients in the SHOCK trial who underwent emergency revascularization received coronary artery bypass surgery, an observation that reflects the complex and extensive CAD in these high-risk patients. Among CS patients with AMI, greater mortality reduction was achieved with revascularization of left main coronary artery (~80%) lesions, and less in those with lesions in the circumflex, left anterior descending arteries, and the right coronary arteries (~40%). Subsequent trials such as CULPRIT-SHOCK evaluated different PCI strategies among patients with CS associated with AMI, and demonstrated lower mortality for patients who initially underwent PCI of the culprit lesion only compared to those who underwent immediate multivessel PCI. Correspondingly, timely culprit lesion PCI is the preferred method of reperfusion for AMI in CS with consideration of staged revascularization of other lesions later. However, the subject of LV unloading with MCS prior to multivessel revascularization has been of current interest as recent data from the National Cardiogenic Shock Initiative showed comparable outcomes for culprit lesion only and multivessel PCI strategies. At present, multivessel PCI in CS patients currently remains a class IIb recommendation according to guidelines.

Apart from early revascularization, management recommendations for patients with AMI-CS are derived from evidence from hemodynamically stable AMI patients or alternative forms of circulatory shock. Patients should receive full-dose aspirin, intravenous unfractionated heparin, and consideration of a P2Y12 inhibitor (eg, clopidogrel, ticagrelor, or cangrelor) unless contraindicated. Beta-blockers and angiotensin-converting enzyme (ACE) inhibitors should initially be avoided until hemodynamic stability is achieved. Like other forms of CS, treatment with vasopressors and inotropes may be needed; however, the lowest dose needed to support organ perfusion should be used as these agents can increase afterload and oxygen demand for the failing myocardium. Additionally, among patients with hypovolemia or active bleeding, judicious fluid administration may be helpful if cardiac preload is insufficient to maintain adequate SV. Furthermore, AMI with CS may be associated with SIRS, or evolve into “hemo-metabolic phase,” and demonstrate reduced SVR. In this setting, the sole use of inotropes, which increase CO but decrease SVR, may not adequately

address shock. Lastly, if a patient develops refractory shock despite the use of vasopressors and inotropes or is not expected to adequately respond to medical therapies, timely escalation of support with temporary MCS devices may be appropriate (detailed later).

Cardiogenic Shock due to Acute-on-Chronic Decompensated Heart Failure

Management of CS due to acute-on-chronic systolic HF should focus on the use of inotropes such as dobutamine or milrinone (Table 4.4) to enhance CO. Both agents increase CO by enhancing myocardial contractility and reducing cardiac afterload. However, each should be used with caution in patients with significant hypotension (eg, systolic BP <80 mm Hg) or low intracardiac filling pressures. In this case, the combination with norepinephrine or epinephrine may be more beneficial to maintain BP and systemic perfusion. Accurate assessment of volume status is critical for the management of CS in the setting of decompensated HF. Judicious diuresis with a goal CVP of 8 to 12 mm Hg may help reduce RV distention, ventricular dilation, and improves ventricular-arterial coupling. However, excessive diuresis may dramatically impair CO, even to the point of hemodynamic collapse, as these patients are highly dependent on preload and require higher filling pressures to maintain SV. In select patients with increased SVR and systolic BP of >100 mm Hg, pure vasodilatory agents such as nitroprusside can improve CO by reducing cardiac afterload.

Cardiogenic Shock: Recovery, Escalation, or Palliation

CS patients require constant monitoring and reassessment in an ICU setting. During and after the stabilization process, shared decision-making among a multidisciplinary team of intensivists, interventionalists, advanced HF cardiologists, cardiothoracic surgeons, critical care nursing, and palliative care specialists is essential. Serial assessment of vital signs, physical exam, laboratories (eg, serum lactate), cardiac imaging parameters (eg, LVOT VTI), and data provided by SGCs (eg, CO by Fick equation or thermodilution) is important to identify patients who will require more hemodynamic support. For patients showing signs of clinical improvement and favorable hemodynamics (eg, CI >2.2 L/min/m^2, cardiac power >0.6 W, PAPi >1.0, RAP <15 mm Hg, pulmonary capillary wedge pressure [PCWP] <15 mm Hg), a trial of decreased support with weaning of inotropes and vasopressors may be appropriate. Conversely, for SCAI stage D or E patients who exhibit signs of refractory shock (eg, increasing lactate,

persistently low $ScvO_2$, persistent hypotension, CI <2.2 L/min/m^2, and cardiac power <0.6 W), MCS should be promptly considered to prevent further decompensation and multiorgan failure.

The decision to add MCS should be discussed via a multidisciplinary team to decide the appropriateness of escalation, while carefully weighing the associated risks and expected benefits. Common contraindications to temporary MCS include poor vascular access options due to severe peripheral vascular disease, anoxic brain injury, end-stage organ damage, and lack of alignment with a patient's stated goals of care. Ideally, temporary MCS is used as a bridge-to-recovery or to other more durable therapies such as a surgically implanted left ventricular assist device (LVAD) or heart transplantation. There are several options for temporary MCS including intra-aortic balloon pump (IABP), Impella, TandemHeart, and venoarterial (VA) extracorporeal membrane oxygenation (ECMO). The individual parameters and benefits of these devices are highlighted in Table 4.5. Choices for specific MCS modalities are driven by the CS phenotype and the amount of support required. After MCS initiation, frequent multimodality monitoring is required to assess therapeutic response, identify complications, and gauge appropriateness of device continuation or weaning.

TABLE 4.5 Characteristics of Temporary Mechanical Support

	IABP	Impella (2.5, CP, 5.0, 5.5)	Impella RP	TandemHeart	VA ECMO
Flow	0.5-1.0 L/min	2.5-5.5 L/min	2-4 L/min	3.5-5.0 L/min	4-7 L/min
Cannula size	7-8 Fr	13-14 Fr 5.0:21 Fr	22 Fr	Vein: 21 Fr Artery: 12-17 Fr	Vein: 18-21 Fr Artery: 14-16 Fr
Durability	14+ d	7-10 d	14 d	≤14 d	14+ d
SVR	↓	↓	+/−	↑	↑↑↑
LV EDP	↓	↓	↑	↓↓	↔

	IABP	Impella (2.5, CP, 5.0, 5.5)	Impella RP	TandemHeart	VA ECMO
Cardiac power	↑	↑↑	↑	↑↑	↑↑
Myocardial O_2 demand	↓	↓↓	↓	↓	↔
Contraindications	Significant AI Severe PAD Aortic aneurysm Sepsis	Mechanical AV LV thrombus VSD Severe PAD Sepsis	RA/RV thrombus Mechanical valve IVC filter Severe PH Sepsis	Significant AI VSD Severe PAD	Aortic dissection Severe PAD Substantial AI

AI, aortic insufficiency; AV, aortic valve; Fr, French; IABP, intra-aortic balloon pump; IVC, inferior vena cava; LV, left ventricle; LV EDP, left ventricular end-diastolic pressure; PAD, peripheral arterial disease; PH, pulmonary hypertension; PVR, peripheral vascular resistance; RA, right atrium; RV, right ventricle; SVR, systemic vascular resistance; VA ECMO, venoarterial extracorporeal membrane oxygenation; VSD, ventricular septal defect.

Intra-aortic Balloon Counterpulsation. The intra-aortic balloon counterpulsation is the most extensively studied and utilized form of MCS for CS. The IABP is a balloon-tipped catheter that is placed via an accessible artery, usually the femoral artery, into the descending aorta. During diastole, the balloon inflates with helium gas, which augments diastolic pressure and increases coronary perfusion. During systole, the balloon deflates rapidly, creating a temporary vacuum that reduces afterload and improves LV ejection. Thus, intra-aortic balloon counterpulsation simultaneously augments central aortic pressure and vital organ perfusion (including coronary blood flow) while reducing afterload and myocardial oxygen demand. Early IABP support can be beneficial as a bridge-to-recovery, such as in the setting of transient myocardial stunning, or as a bridge-to-decision for more advanced HF therapies, including durable LVAD or cardiac transplantation. It should be considered as an early intervention for patients with CS in whom there are none of the following contraindications: severe aortic insufficiency, severe peripheral vascular disease, aortic dissection, bleeding diathesis, or sepsis. Complications include bleeding, acute limb ischemia, thrombocytopenia, and infection.

After the SHOCK II trial was published, IABP use for CS became a class IIb recommendation in the American guidelines and a class III recommendation in the European guidelines. In the SHOCK II trial, 600 patients with CS complicating AMI were randomly assigned to intra-aortic balloon counterpulsation (*n* = 301) or no intra-aortic balloon counterpulsation (*n* = 299). There was no difference between groups in 30-day mortality, the primary end point. Secondary end points, such as time to hemodynamic stabilization, ICU length of stay, lactic acidosis, renal function, vasopressor dose, and treatment duration, were also similar between groups. On the other hand, the IABP group had similar rates of major bleeding, peripheral ischemic complication, stroke, and sepsis to the control group, therefore meeting safety parameters. However, it is important to note that the data from this trial do not apply to patients with CS from acute-on-chronic HF as these patients often gain a larger benefit from these devices.

Percutaneous and Surgical Ventricular Assist Devices

When medical therapy and IABP support do not, or are not expected to, adequately stabilize vital organ perfusion, more advanced forms of MCS may be necessary and should be considered before irreversible end-organ damage occurs. Temporary LVADs can be inserted surgically or percutaneously to improve CO and LV unloading. In suitable patients, a temporary LVAD is used as a bridge to recovery or more definitive treatment options such as a durable LVAD or heart transplantation.

The Impella is a catheter-based microaxial pump that continuously pumps blood from the LV into the ascending thoracic aorta. It may be percutaneously inserted into the femoral artery or surgically grafted to the aorta via an arterial cut down of an axillary artery. The catheter is advanced retrograde across the aortic valve, and the inlet at the distal catheter is positioned within the LV. The device can deliver 2.5 to 5.5 L/min of CO depending on model catheter size. Experience with Impella catheters continues to grow and their impact on patient hemodynamics has been demonstrated in multiple trials and registries. Nonetheless, their impact on clinical outcomes and survival compared to IABP in CS patients remains unclear. The 2017 IMPRESS trial was a randomized controlled trial of 48 patients with severe CS complicating AMI randomized to Impella CP (*n* = 24) or IABP (*n* = 24). There was no difference in the primary end point of 30-day mortality, and the 6-month mortality rate was also similarly very high for both groups (approximately 50%). Contraindications to Impella insertion include aortic regurgitation, aortic dissection/aneurysm, severe peripheral vascular

disease, bleeding diathesis, LV thrombus, and sepsis. Device-related complications, including bleeding, vascular compromise, thromboembolic events, and infections, may pose additional challenges to CS patients.

The TandemHeart System involves a large-bore venous catheter inserted into the left atrium via transseptal puncture for withdrawal of oxygenated blood and an arterial catheter placed in the femoral artery for blood return. The catheters are connected to an extracorporeal centrifugal pump that can provide up to 5.0 L/min of flow. TandemHeart can significantly augment MAP while reducing LV filling pressures and myocardial oxygen demand. Its use in CS was studied in two small multicenter trials to which TandemHeart use improved patient hemodynamics but did not demonstrate a difference in patient mortality compared to intra-aortic balloon counterpulsation. Contraindications to TandemHeart use include aortic insufficiency, VSD, and severe peripheral vascular disease. Device-related complications include bleeding, critical limb ischemia, tamponade, arrhythmias, and residual atrial septal defect.

The Impella RP is a microaxial pump designed to provide temporary support for the acutely failing RV. This device is placed through percutaneous venous access and is positioned with its inflow section within the right atrium and outflow section in the pulmonary artery to allow for bypass of the right ventricle. Thus, the Impella RP can simultaneously unload and bypass a failing RV. Greater than 4 L/min of flow may be achieved. Contraindications to insertion include intracardiac thrombi, inferior vena cava filter, or mechanical prostheses (eg, mechanical tricuspid valve replacement). The most common device-related complications include bleeding, thrombus formation, and hemolysis.

Extracorporeal Life Support With Extracorporeal Membrane Oxygenation. ECMO is a modified form of cardiopulmonary bypass designed to support both cardiac and pulmonary function. Specifically, VA ECMO can provide gas exchange (ie, oxygenation and decarboxylation) and total systemic circulation CS patients for days to several weeks. Its use has increased dramatically, especially in patients with refractory CS or circulatory arrest. A VA ECMO circuit is comprised of a centrifugal pump that drives blood from the patient's venous system through an externalized membrane oxygenator system, before returning it to the patient's arterial system. Peripheral cannulation configurations for VA ECMO vary but are typically the femoral vein-to-femoral artery or internal jugular vein-to-femoral artery. Peripheral ECMO can be placed at the bedside, making it particularly useful in patients

with the highest acuity (eg, SCAI class E). On the other hand, central ECMO requires a partial sternotomy with placement of the venous cannula in the RA or vena cava with arterial cannulation directly into the aorta. This configuration is most commonly used for patients unable to successfully come off of cardiopulmonary bypass following cardiac surgery. Once placed, VA ECMO circulation typically provides 4 to 7 L/min of flow, representing the highest that may be achieved by contemporary MCS devices. Distinct advantages of VA ECMO over other temporary MCS devices are its ability to (i) oxygenate blood for hypoxemic patients and (ii) simultaneously provide support for both the left and right ventricles.

Common complications include limb ischemia, bleeding, hemolysis, stroke, and infection. In addition, it is important to recognize that the VA ECMO circuit introduces highly pressurized blood flow into systemic arteries or aorta, which greatly increases LV afterload. The increased afterload prevents efficient LV ejection leading to stagnation of blood in the ventricle and high LV filling pressures, which can lead to aortic root or intracardiac thrombus formation and pulmonary edema. Therefore, unloading the LV to reduce LV filling pressures (ie, LV venting) may be necessary. LV venting can be accomplished using percutaneous devices, such as an Impella or IABP, or surgically via atrial septostomy or direct catheter placement into a pulmonary vein or through the LV apex. Lastly, a rare complication known as “Harlequin Syndrome” (or “North-South Syndrome”) may occur in patients with peripheral VA ECMO configurations and severely impaired gas exchange in the lungs. In this complication, the “mixing cloud,” or merger point of oxygenated blood returned from the VA ECMO circuit and inadequately oxygenated blood expelled from the native heart, is distally displaced in the descending thoracic or abdominal aorta. Thus, the presence of severely deoxygenated blood prevails proximally while the lower half of the body receives well-oxygenated blood from the ECMO circuit. As a result, differential hypoxia emerges and manifests as bluish discoloration in the head, neck, and upper extremities of the patient.

There have been attempts to determine the optimal timing of VA ECMO use in severe CS. The Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock (ECMO-CS) study investigated the role of immediate VA ECMO implantation in high-risk CS patients (SCAI stage D or E) versus a conservative approach with initial inotropes and vasopressors. Notably, patients in the conservative management arm could be placed on VA ECMO support if their clinical status worsened. There was no difference between the study groups for the composite end point of death, resuscitated

arrest, and additional MCS needed at 30 days, suggesting that VA ECMO should be reserved for CS patients with worsening hemodynamics despite initial medical stabilization efforts.

Conclusion

- CS is a state of end-organ hypoperfusion and tissue hypoxia due to reduced CO despite adequate intracardiac filling pressures.
- Mortality of CS remains high and prompt recognition is essential for management, as timely and appropriate treatment can significantly reduce mortality.
- After prompt recognition, CS patients require rapid stabilization with medical therapy, including vasopressors, inotropes, and volume resuscitation.
- Accurate assessment of volume status is critical for the management of CS in the setting of decompensated HF.
- Revascularization for CS complicating AMI improves outcomes; therefore, rapid diagnosis and referral for left heart catheterization are necessary.
- In cases of severe and refractory CS, temporary MCS devices should be considered as a bridge-to-recovery option or as a bridge to consider more durable options including LVAD or cardiac transplantation.

SUGGESTED READINGS

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5 Anaphylactic Shock

Matthew McCauley

Traditionally, *anaphylaxis* refers to the often-life-threatening clinical manifestations of the immunoglobulin E (IgE)-mediated immediate hypersensitivity reaction, involving mast cell and basophil degranulation with release of histamine, tryptase, prostaglandins, and leukotrienes, that occurs following exposure to various substances. Similar clinical manifestations also occur via nonimmunologic mechanisms such as direct complement activation, direct mast cell activation, and direct release of basophil mediators. These nonallergic mechanisms, previously known as *anaphylactoid* reactions, are clinically indistinguishable from anaphylaxis. Different substances trigger allergic and nonallergic anaphylaxis and are outlined in Table 5.1.

TABLE 5.1 Causes of Anaphylaxis (Substances Are Paired With the Most Common Associated Mechanism)

Anaphylaxis (immune mediated)
Foods (especially nuts, peanuts, eggs, fish, shellfish, alpha-gal from mammalian meat, and cow's milk)
Antibiotics (especially penicillin; low cross-reactivity to cephalosporins and other penicillins)
Vaccines
Anesthetics
Insulin, progesterone, and other hormones
Antitoxins
Blood and blood products
Insect stings and bites (bee, wasp, and ant)
Snake bites
Latex
Immune globulins
Nonimmune related

Nonsteroidal anti-inflammatory drugs (especially aspirin)
Opiates
Sulfites
Radiocontrast media
Neuromuscular blocking agents (curoniums and succinylcholine)
Antisera
Heparin and protamine neutralization of heparin
Hemodialysis membranes

Reactions can develop within minutes to hours after exposure to a trigger, with more rapid reactions occurring with parenteral exposures. Initial symptoms include skin flushing, pruritus, and a sense of doom. Characteristic clinical manifestations of varying severity develop involving the skin, eyes, respiratory system, gastrointestinal (GI) tracts, cardiovascular system, and central nervous systems, as listed in Table 5.2. Cardiovascular collapse (shock) occurs in approximately 30% of cases and results from (a) hypovolemia induced by increased vascular permeability and capillary leak, (b) peripheral vasodilation, (c) myocardial depression from angioedema and hypoxemia, and (d) bradycardia. About half of patients exhibit respiratory symptoms, which can progress to respiratory failure from severe upper airway edema, bronchospasm, and the combination of cardiogenic and noncardiogenic pulmonary edema. Biphasic reactions, characterized by a second episode of symptoms, occur in up to 20% of patients. If this occurs, it does so without reexposure to the trigger within the first hour to 8 hours following the initial episode, but cases have been reported with delays up to 72 hours.

TABLE 5.2 Clinical Manifestations of Anaphylaxis and Laboratory Tests

Clinical Manifestations:	
Eyes	Skin

Clinical Manifestations:	
Pruritus Lacrimation Conjunctival erythema Periorbital edema	Pruritus Flushing Urticaria Angioedema
Cardiovascular	Respiratory
Hypotension Tachycardia (bradycardia when severe) Arrhythmias Cardiac arrest Paradoxical hypertension (in presence of beta-adrenergic blockers)	Dyspnea Stridor/Wheezing/Hoarseness Difficulty swallowing Pulmonary edema
Gastrointestinal	Neurologic
Nausea/vomiting Diarrhea Abdominal pain	Anxiety and “sense of doom” Presyncope and syncope Seizures
Laboratory Tests	
Total serum or plasma tryptase	Plasma histamine
Mature beta-tryptase	Platelet-activating factor

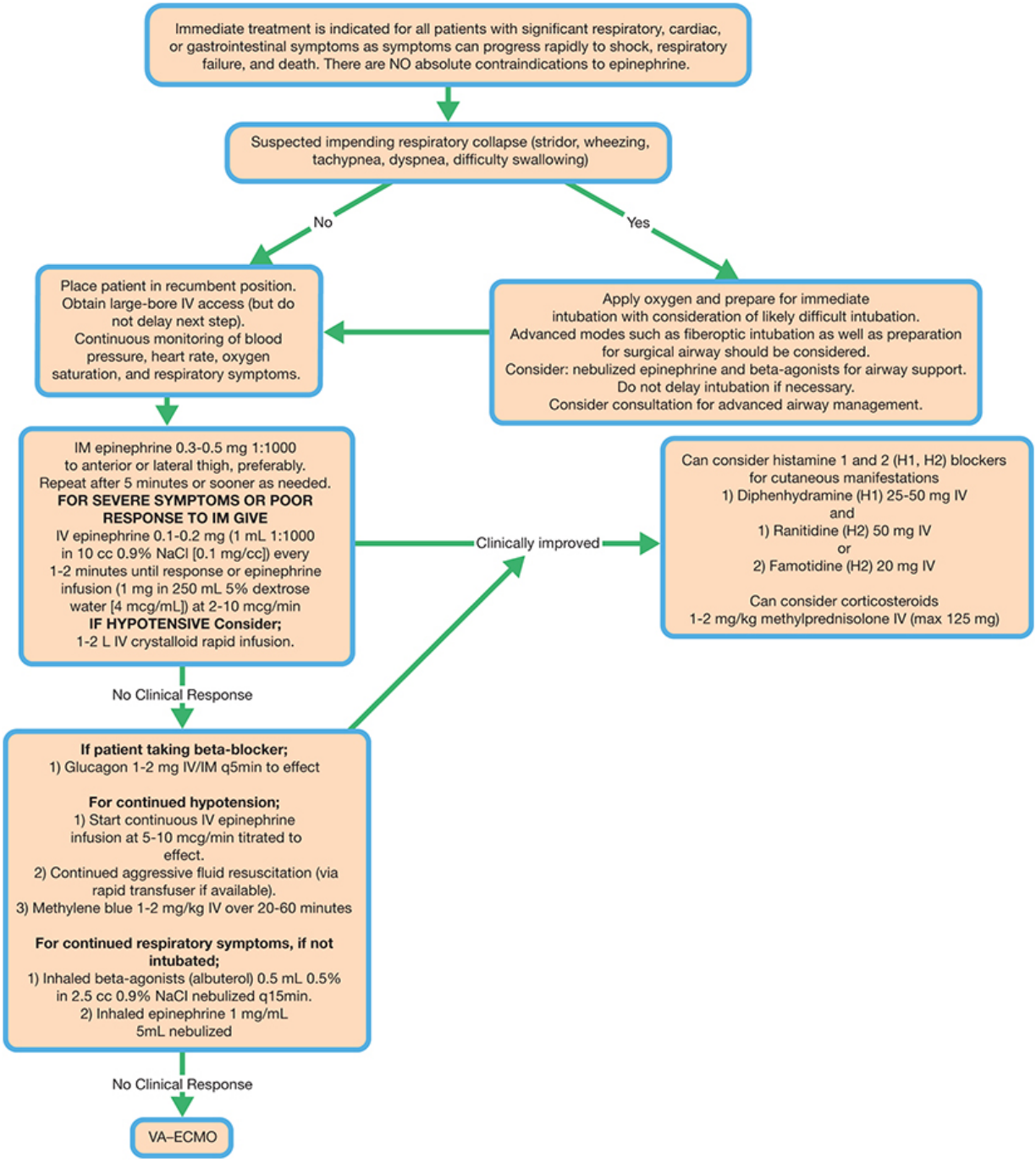
The diagnosis of anaphylaxis is clinical and there is no universally agreed upon criteria. The Modified NIAID/FAAN consensus definition establishes three clinical criteria that include the acute onset of mucocutaneous involvement that is combined with respiratory compromise, compromised blood pressure, or signs of end-organ dysfunction after exposure to a possible allergen. In order to be sufficiently sensitive, this definition also includes the rapid onset of the combination of mucocutaneous symptoms, respiratory compromise, reduced blood pressure, or persistent GI symptoms that occur following exposure to a likely allergen. Finally, it must be noted that this definition also includes isolated hypotension after the

exposure to a known allergen. When prospectively validated, this definition was found to be 95% sensitive and other definitions have been found to have similar sensitivities. Thus, a high level of clinical suspicion must be maintained as no case definition is perfectly sensitive.

A working diagnosis of anaphylaxis should involve a broad differential including urticaria, status asthmaticus, vancomycin infusion reaction, scombroid reaction to fish ingestion, carcinoid, pheochromocytoma, mastocytosis, vocal cord dysfunction, and panic attacks as a diagnosis of exclusion. Obtaining serum levels of tryptase (especially the beta subtype) and histamine will not inform immediate management but can help retrospectively establish the diagnosis. Tryptase levels peak approximately 60 to 90 minutes after onset of symptoms and remain elevated for 1 to 6 hours after the event, but serum histamine levels fall within 30 to 60 minutes. A 24-hour urine *N*-methyl histamine level compared to a later baseline can be a helpful alternative. Patients should be questioned about exposure to potential triggers, but no substance is identified in up to 60% of cases.

Treatment is outlined in Algorithm 5.1 and is based on the joint recommendations of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology. The use of epinephrine to reverse the respiratory and cardiovascular effects of anaphylaxis remains the cornerstone of pharmacologic management. There are no contraindications to the use of epinephrine, and numerous studies have shown that it is underused in emergency treatment, with delay resulting in higher rates of biphasic reactions, shock, respiratory failure, hypoxic encephalopathy, and death. Guidelines recommend 0.3 to 0.5 mg to be given intramuscularly (IM) into the anterolateral thigh repeated every 5 to 15 minutes if symptoms persist. IM injection of epinephrine has been associated with fewer complications in several studies compared to intravenous (IV) administration, which should be reserved for refractory cases of anaphylactic shock.

ALGORITHM 5.1 Acute Treatment of Patients With Anaphylaxis


Immediate treatment is indicated for all patients with significant respiratory, cardiac, or gastrointestinal symptoms as symptoms can progress rapidly to shock, respiratory failure, and death. There are NO absolute contraindications to epinephrine.
Suspected impending respiratory collapse (stridor, wheezing, tachypnea, dyspnea, difficulty swallowing)
No
Yes
Place patient in recumbent position. Obtain large-bore IV access (but do not delay next step). Continuous monitoring of blood pressure, heart rate, oxygen saturation, and respiratory symptoms.
Apply oxygen and prepare for immediate intubation with consideration of likely difficult intubation. Advanced modes such as fiberoptic intubation as well as preparation for surgical airway should be considered. Consider: nebulized epinephrine and beta-agonists for airway support. Do not delay intubation if necessary. Consider consultation for advanced airway management.
IM epinephrine 0.3-0.5 mg 1:1000 to anterior or lateral thigh, preferably. Repeat after 5 minutes or sooner as needed. FOR SEVERE SYMPTOMS OR POOR RESPONSE TO IM GIVE IV epinephrine 0.1-0.2 mg (1 mL 1:1000 in 10 cc 0.9% NaCl [0.1 mg/cc]) every 1-2 minutes until response or epinephrine infusion (1 mg in 250 mL 5% dextrose water [4 mcg/mL]) at 2-10 mcg/min IF HYPOTENSIVE Consider; 1-2 L IV crystalloid rapid infusion.
Clinically improved
Can consider histamine 1 and 2 (H1, H2) blockers for cutaneous manifestations 1) Diphenhydramine (H1) 25-50 mg IV and 1) Ranitidine (H2) 50 mg IV or 2) Famotidine (H2) 20 mg IV
Can consider corticosteroids 1-2 mg/kg methylprednisolone IV (max 125 mg)
No Clinical Response
If patient taking beta-blocker; 1) Glucagon 1-2 mg IV/IM q5min to effect
For continued hypotension; 1) Start continuous IV epinephrine infusion at 5-10 mcg/min titrated to effect. 2) Continued aggressive fluid resuscitation (via rapid transfuser if available). 3) Methylene blue 1-2 mg/kg IV over 20-60 minutes
For continued respiratory symptoms, if not intubated; 1) Inhaled beta-agonists (albuterol) 0.5 mL 0.5% in 2.5 cc 0.9% NaCl nebulized q15min. 2) Inhaled epinephrine 1 mg/mL 5mL nebulized
No Clinical Response
VA–ECMO

Respiratory distress signaling impending airway compromise may complicate presentations of anaphylaxis, the management of which should be focused on immediate administration of IM epinephrine.

Nebulized epinephrine and beta-agonists may be considered for persistent stridor or bronchoconstriction, respectively, but should not delay securing the airway if indicated. Worsening angioedema, bronchorrhea, and hemodynamic instability refractory to epinephrine can predispose to difficult airway management, so early endotracheal intubation should be considered in cases of persistent respiratory distress.

Other medications are routinely given for the management of anaphylaxis with limited levels of evidence. Steroids are given as an initial dose of 1 to 2 mg/kg of IV methylprednisolone, or equivalent, and continued for up to 4 days (IV or orally). Multiple society guidelines support the use of steroids as an adjuvant therapy, citing the physiologic underpinning of steroid administration and limited evidence that they may prevent biphasic reactions. Recent reviews have refuted this claim. Similarly, while the administration of antihistamines can be considered as an adjunct to treat urticaria and itching, the evidence that they have a role in preventing biphasic reactions is poor and their administration should not delay (or be considered an alternative to) timely epinephrine administration.

While most patients will improve with epinephrine, cases of anaphylaxis that do not improve with at least 300 mcg of epinephrine are considered refractory and may require additional therapies. While the IM route is preferred for routine administration, continuous IV administration can be considered for persistent hypotension. In this circumstance, crystalloid infusion is also recommended with a low quality of evidence, and multiple boluses may be required. Glucagon bolus and infusion can be considered for patients with persistent hypotension and a history of beta-blocker exposure, but care must be taken to monitor for nausea and vomiting. Additionally, methylene blue can be considered for refractory vasoplegia. In cases of cardiac arrest or truly refractory hypotension unresponsive to all other supportive care, consultation for temporary mechanical support with venoarterial extracorporeal membrane oxygenation can be pursued.

There is no consensus regarding the appropriate observation period following an episode of anaphylaxis. The data regarding the

likelihood of biphasic reactions are poor but patients who require multiple doses of epinephrine, present in shock, or have delays to administration of epinephrine warrant longer periods of observation than more routine presentations. On discharge, patients should be referred to an allergist for testing and monitoring and provided with home epinephrine self-injectors.

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6 Mechanical Causes of Shock

John C. Grotberg

Mechanical shock can be precipitated by an array of syndromes that produce an acute loss of pulmonary vascular cross-sectional area, either by direct obstruction of pulmonary vasculature or through vasoconstriction driven by vasoactive mediators. The end result is an acute rise in pulmonary vascular resistance (PVR), which leads to right ventricular (RV) strain, RV failure, and shock. *Mechanical shock* is also called *obstructive shock*; these terms are used interchangeably in the literature. Cardiac tamponade, discussed in Chapter 4, Cardiogenic Shock, can also be considered a mechanical cause of shock. However, its pathophysiology is distinct from the other forms of shock discussed here. Although the various etiologies of shock are discussed in isolation in this manual, it is important to recognize that several forms of shock may be present at the same time.

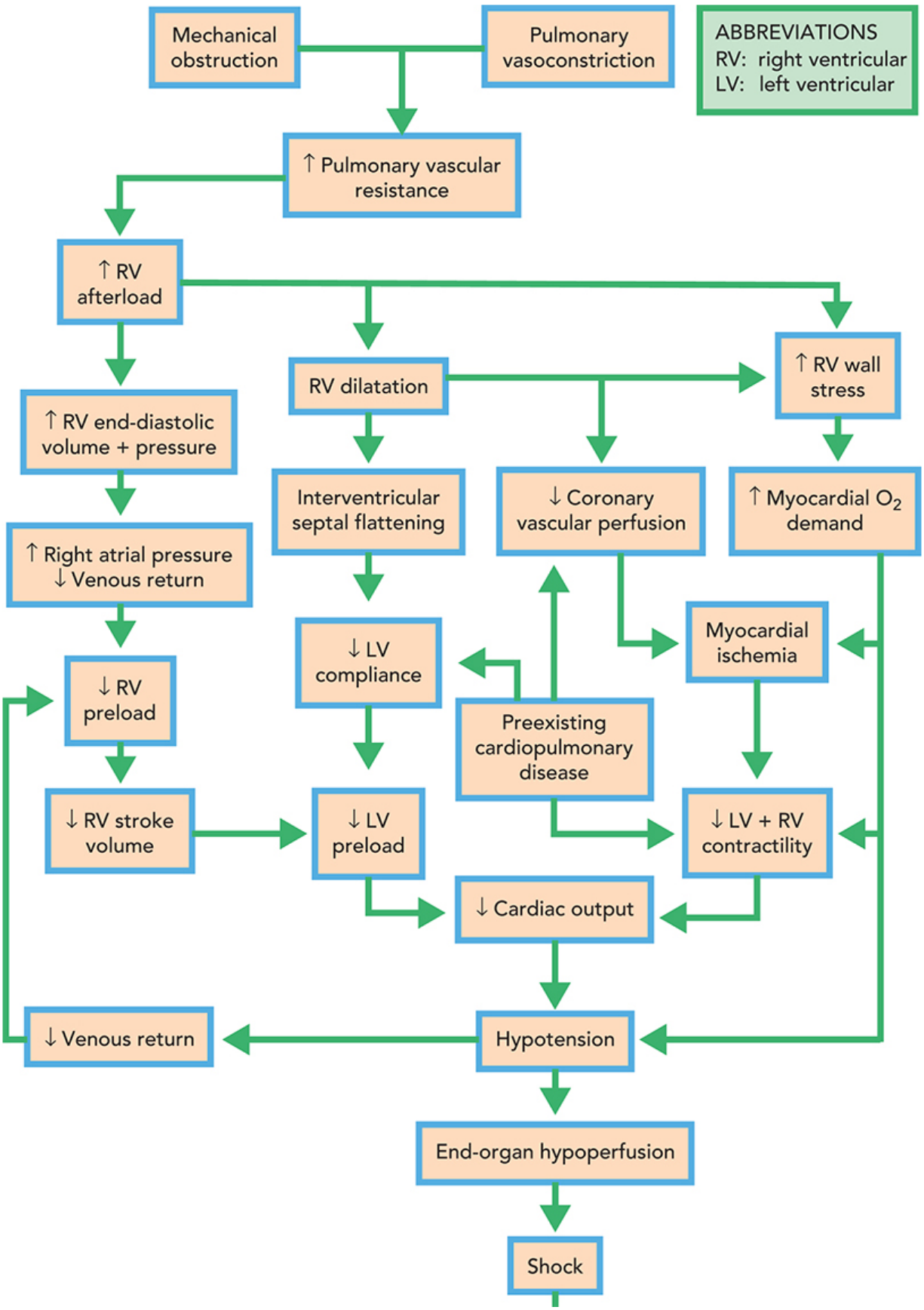
This discussion will focus on four major etiologies of mechanical shock: (1) massive pulmonary embolism (PE), (2) air embolism, (3) fat embolism, and (4) amniotic fluid (AF) embolism. The degree of hemodynamic compromise caused by any of these causes of mechanical shock is determined by (1) the magnitude of pulmonary arterial vascular obstruction and/or vasoconstriction, (2) RV performance and reserve, and (3) preexisting cardiopulmonary disease (CPD). For example, a segmental pulmonary embolus normally survivable in an otherwise healthy postpartum patient may produce mechanical shock in a patient with preexisting pulmonary arterial hypertension and marginal RV function.

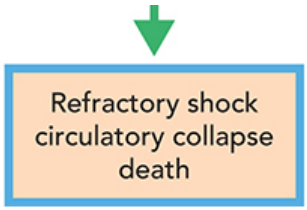
The pulmonary circulation is normally a high-capacitance, low-resistance circuit. In general, a RV cannot acutely compensate for a mean pulmonary arterial pressure (mPAP) greater than 40 mm Hg. Therefore, the finding of mPAP values greater than 40 mm Hg

without clinical signs of RV failure suggests a subacute or chronic cause of pulmonary arterial hypertension. In the absence of preexisting CPD, the increase in RV afterload and mPAP is directly proportional to the magnitude of pulmonary vascular obstruction and/or vasoconstriction. Echocardiographic findings of acute RV dysfunction may be evident following a 25% to 30% reduction in pulmonary vascular cross-sectional area. However, the degree of obstruction necessary to cause hemodynamic compromise and shock may be much lower in a patient with preexisting CPD.

Without aggressive intervention, an acute elevation in PVR beyond the capacity of RV compensation precipitates a deleterious chain of events that ends in refractory shock, circulatory collapse, and death. Algorithm 6.1 illustrates the interdependent nature of the multiple factors that contribute to mechanical shock. Successful management of mechanical shock syndromes requires early recognition and rapid initiation of supportive measures to restore hemodynamic stability and prevent end-organ dysfunction.

ALGORITHM 6.1 **Pathophysiology of Mechanical Shock**


Mechanical obstruction
Pulmonary vasoconstriction
ABBREVIATIONS
RV: right ventricular
LV: left ventricular
↑ Pulmonary vascular resistance
↑ RV afterload
↑ RV end-diastolic volume + pressure
↑ Right atrial pressure
↓ Venous return
↓ RV preload
↓ RV stroke volume
RV dilatation
Interventricular septal flattening
↓ LV compliance
↓ LV preload
↑ RV wall stress
↓ Coronary vascular perfusion
↑ Myocardial O2 demand
Myocardial ischemia
Preexisting cardiopulmonary disease
↓ LV + RV contractility
↓ Cardiac output
↓ Venous return
Hypotension
End-organ hypoperfusion
Shock



Common clinical findings in mechanical shock states include tachycardia, hypotension, and signs of end-organ hypoperfusion (i.e., decreased urine output, cool and mottled extremities, and altered mental status). Physical examination may reveal signs of decompensated RV failure, including jugular venous distention, tricuspid regurgitation murmur, accentuated P2, hepatojugular reflux, and Kussmaul sign. Dysregulation of ventilation-perfusion matching results in hypoxemia and tachypnea. In catastrophic cases, ventricular fibrillation, pulseless electrical activity, or asystole may be the initial presentation.

Diagnostically, sinus tachycardia is frequently seen on electrocardiogram (ECG), with or without changes suggestive of RV strain and myocardial ischemia. Echocardiographic signs of RV dysfunction, including RV dilation, hypokinesis, a low tricuspid annular plane systolic excursion (TAPSE) of less than 17 mm, tricuspid regurgitation, and flattening of the interventricular septum, may also be present. Common laboratory findings include hyponatremia, elevated serum brain natriuretic peptide (BNP), increased markers of myocardial injury (troponin T or I), and elevated lactate.

The following sections discuss the unique features, pathophysiology, and management of four common mechanical shock syndromes. Table 6.1 contains a list of risk factors and presenting signs and symptoms for each syndrome.

TABLE 6.1 Risk Factors and Common Manifestations of Mechanical Shock States

	Risk Factors	Common Signs and Symptoms

	Risk Factors	Common Signs and Symptoms
Massive pulmonary embolism	• Immobilization • Surgery within last 3 mo • Prior history of VTE • Malignancy • Chronic cardiopulmonary disease • Trauma • Obesity • Central venous catheters • Hypercoagulable state	• Pleuritic chest pain • Respiratory distress • Cough • Wheezing • Hemoptysis • Hypoxemia • Cyanosis • Fever
Air embolism syndrome	• Open surgical site above RA (craniotomy, cesarean section) • Use of medical gases in laparoscopic or endoscopic procedures • Volume depletion • Barotrauma • Pulmonary vasodilators • Biopsy of airway or lung parenchyma • Venous access devices • Contrast injection • Trauma	• Anxiety • Sense of impending doom • Chest pain • Respiratory distress • Wheezing • Cyanosis • Hypoxemia • Gasp reflex • Mill-wheel murmur on auscultation • Agitation, delirium, seizure activity (arterial gas embolization)

	Risk Factors	Common Signs and Symptoms
Fat embolism syndrome	• Blunt force trauma resulting in long bone and pelvic fractures • Orthopedic procedures • Extensive rib fractures • Burn injury • Acute pancreatitis • Diabetes mellitus • Sickle cell anemia • Liposuction • Parenteral lipid infusion	• Agitation • Delirium • Seizure activity • Fevers and chills • Chest pain • Respiratory distress • Wheezing • Cyanosis • Hypoxemia • Petechial rash involving axilla and upper trunk
Amniotic fluid embolism syndrome	• Pregnancy • Peripartum • Postpartum (up to 48 h) • Difficult labor • Use of labor induction agents • Amniocentesis • First or second trimester abortion • Trauma	• Agitation and delirium • Seizure activity • Fevers and chills • Nausea and vomiting • Respiratory distress • Wheezing • Chest pain • Cyanosis • Hypoxemia • Profuse hemorrhage with no obvious structural cause • Fetal bradycardia or late decelerations

RA, right artery; VTE, venous thromboembolism.

Pulmonary Embolism

Venous thromboembolism (VTE) is a common complication in critically ill medical and surgical patients. Most intensive care unit

(ICU) patients have multiple major risk factors for VTE, including trauma, prolonged immobilization, malignancy, and indwelling vascular access devices. Clinical studies in medical ICUs have shown up to one-third of patients not receiving deep venous thrombosis prophylaxis will eventually develop VTE at some point during their hospital course. Approximately 5% to 10% of patients with VTE develop PE, with approximately 10% of these cases causing hemodynamically significant or massive PE. The presence of shock in the setting of PE is associated with a 5- to 7-fold increase in mortality. Patients presenting with cardiopulmonary arrest have mortality rates exceeding 65%.

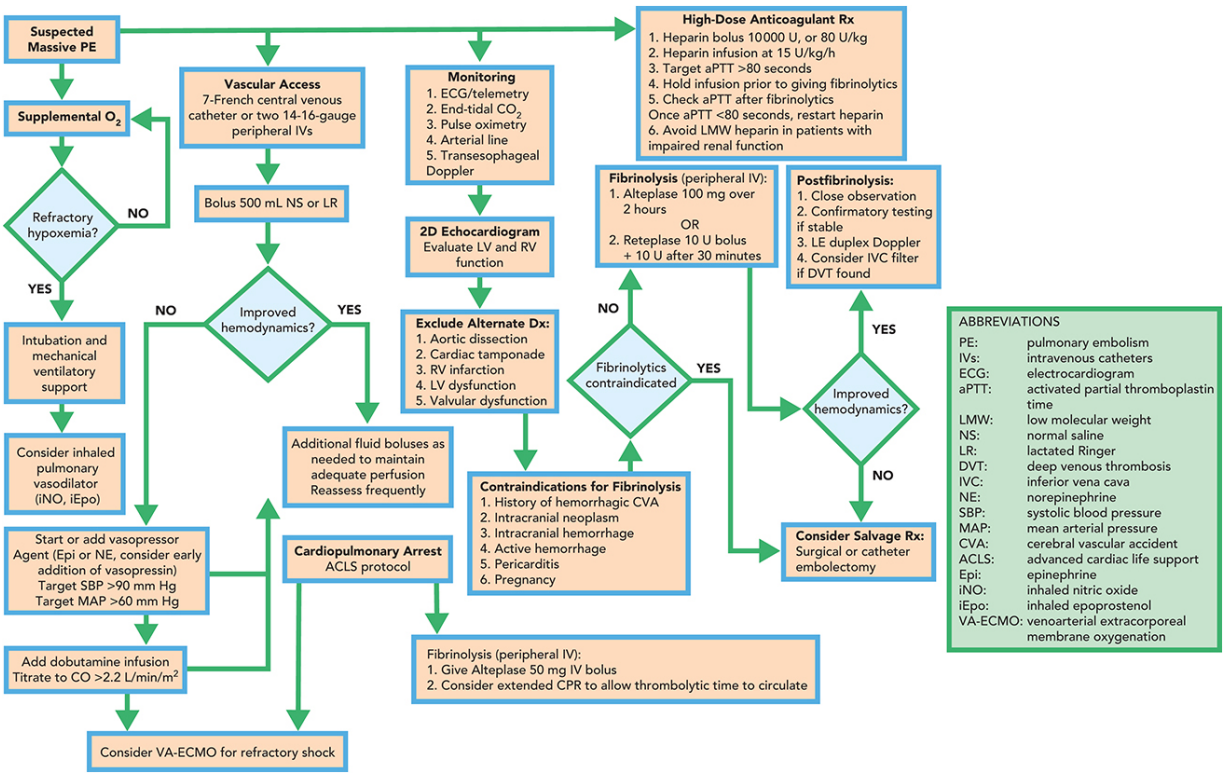
Bedside 2D echocardiography is a useful diagnostic tool for evaluating hemodynamic status in patients with suspected massive PE. Alternative diagnoses, such as cardiomyopathy, valvular disease, cardiac tamponade, and aortic dissection, can be quickly excluded from the differential diagnosis. McConnell sign, a classic echocardiographic sign of massive PE, is characterized by global RV hypokinesis with relative sparing of the apical segments. The 60/60 sign, defined as a pulmonary artery systolic pressure (PASP) less than 60 mm Hg and a pulmonary acceleration time (PAT) of less than 60 msec, may also be present in acute failure of the RV secondary to massive PE.

Risk stratification of PE is necessary to determine appropriate therapy. The European Society of Cardiology (ESC) categorizes PE risk as low, intermediate (submassive), and high (massive) based on patient hemodynamics, presence of RV strain on imaging, cardiac biomarkers, and Pulmonary Embolism Severity Index (PESI). Intermediate risk is further subdivided into intermediate-high and intermediate-low risk. Due to the complexity of VTE and the availability of newer catheter-based therapies, many institutions have adopted multidisciplinary pulmonary embolism response teams (PERTs) to aid in risk stratification and therapeutic interventions.

Initiation of therapy should not be delayed for confirmatory diagnostic testing. Treatment should be focused on (1) restoring hemodynamic stability, (2) maintaining adequate oxygenation, and

(3) reducing clot burden and preventing recurrent embolus. A management algorithm for massive PE is shown in Algorithm 6.2.

ALGORITHM 6.2 **Management Algorithm for Massive Pulmonary Embolism**


Suspected Massive PE
Supplemental O2
Refractory hypoxemia?
NO
YES
Intubation and mechanical ventilatory support
Consider inhaled pulmonary vasodilator (iNO, iEpo)
Start or add vasopressor Agent (Epi or NE, consider early addition of vasopressin) Target SBP >90 mm Hg Target MAP >60 mm Hg
Add dobutamine infusion Titrate to CO >2.2 L/min/m2
Consider VA-ECMO for refractory shock
Vascular Access
7-French central venous catheter or two 14-16-gauge peripheral IVs
Bolus 500 mL NS or LR
Improved hemodynamics?
NO
YES
Additional fluid boluses as needed to maintain adequate perfusion Reassess frequently
Cardiopulmonary Arrest
ACLS protocol
Monitoring
1. ECG/telemetry
2. End-tidal CO2
3. Pulse oximetry
4. Arterial line
5. Transesophageal Doppler
2D Echocardiogram
Evaluate LV and RV function
Exclude Alternate Dx:
1. Aortic dissection
2. Cardiac tamponade
3. RV infarction
4. LV dysfunction
5. Valvular dysfunction
Contraindications for Fibrinolysis
1. History of hemorrhagic CVA
2. Intracranial neoplasm
3. Intracranial hemorrhage
4. Active hemorrhage
5. Pericarditis
6. Pregnancy
Fibrinolysis (peripheral IV):
1. Give Alteplase 50 mg IV bolus
2. Consider extended CPR to allow thrombolytic time to circulate
High-Dose Anticoagulant Rx
1. Heparin bolus 10000 U, or 80 U/kg
2. Heparin infusion at 15 U/kg/h
3. Target aPTT >80 seconds
4. Hold infusion prior to giving fibrinolytics
5. Check aPTT after fibrinolytics
Once aPTT <80 seconds, restart heparin
6. Avoid LMW heparin in patients with impaired renal function
Fibrinolysis (peripheral IV):
1. Alteplase 100 mg over 2 hours
OR
2. Reteplase 10 U bolus + 10 U after 30 minutes
NO
Fibrinolytics contraindicated
YES
Improved hemodynamics?
YES
NO
Consider Salvage Rx:
Surgical or catheter embolectomy
Postfibrinolysis:
1. Close observation
2. Confirmatory testing if stable
3. LE duplex Doppler
4. Consider IVC filter if DVT found
ABBREVIATIONS
PE: pulmonary embolism
IVs: intravenous catheters
ECG: electrocardiogram
aPTT: activated partial thromboplastin time
LMW: low molecular weight
NS: normal saline
LR: lactated Ringer
DVT: deep venous thrombosis
IVC: inferior vena cava
NE: norepinephrine
SBP: systolic blood pressure
MAP: mean arterial pressure
CVA: cerebral vascular accident
ACLS: advanced cardiac life support
Epi: epinephrine
iNO: inhaled nitric oxide
iEpo: inhaled epoprostenol
VA-ECMO: venoarterial extracorporeal membrane oxygenation

Multiple randomized controlled trials have addressed the role of thrombolytic (fibrinolytic) therapy versus anticoagulation with unfractionated or low-molecular-weight heparin as initial treatment for PE. In patients with hemodynamic instability, thrombolytic therapy has been associated with faster recovery of RV function and improvement in hemodynamic status. Among patients with “moderately severe” pulmonary emboli, the use of half-dose tissue plasminogen activator (tPA) has been associated with decreased incidence of pulmonary hypertension after 28 months of follow-up. Additionally, a recent meta-analysis demonstrated a decrease in all-cause mortality associated with the combined use of therapeutic anticoagulation and thrombolysis when compared to the use of

therapeutic anticoagulation alone. The risk of major bleeding was increased with thrombolysis, though this association was only significant in patients older than 65 years. For patients with hemodynamic instability, and no contraindications, systemic thrombolysis should be strongly considered. For patients with major contraindications to thrombolytic therapy or unresponsive to pharmacologic thrombolysis, catheter thrombectomy or open surgical embolectomy may be attempted. Patients with intermediate high-risk PE who are at risk for hemodynamic deterioration may be considered for catheter-directed intervention (CDI). Although no randomized, controlled trials have evaluated its effect, the use of extracorporeal membrane oxygenation (ECMO) in patients with hemodynamic instability after acute PE has been shown in a recent systematic review to be associated with a 70% overall survival, regardless of what specific treatment option was used to address the embolism. While more data are needed to guide decision-making, this therapy should be considered in patients with severe shock from pulmonary emboli.

Once hemodynamic stability is restored, definitive diagnosis can be established by computed tomographic angiography or pulmonary angiography. An evaluation for deep venous thrombosis by duplex Doppler ultrasound should be performed with consideration of inferior vena cava filter placement in patients with marginal cardiac function and high clot burden.

Air Embolism

Air embolism syndrome (AES) occurs when gas enters the arterial or venous circulation driven by a pressure gradient favoring entrainment of gas, or through direct injection. Arterial gas embolization may occur through anatomic shunts (eg, patent foramen ovale, vascular malformations), pulmonary vasodilator administration, or if the filtration capacity of the pulmonary circulation is overwhelmed by a large volume of gas entering the venous circulation. Indeed, each case of venous air embolism is a potential

case of arterial air embolism. Arterial AES typically does not cause mechanical shock. However, gas entering the coronary circulation may cause myocardial ischemia and cardiogenic shock.

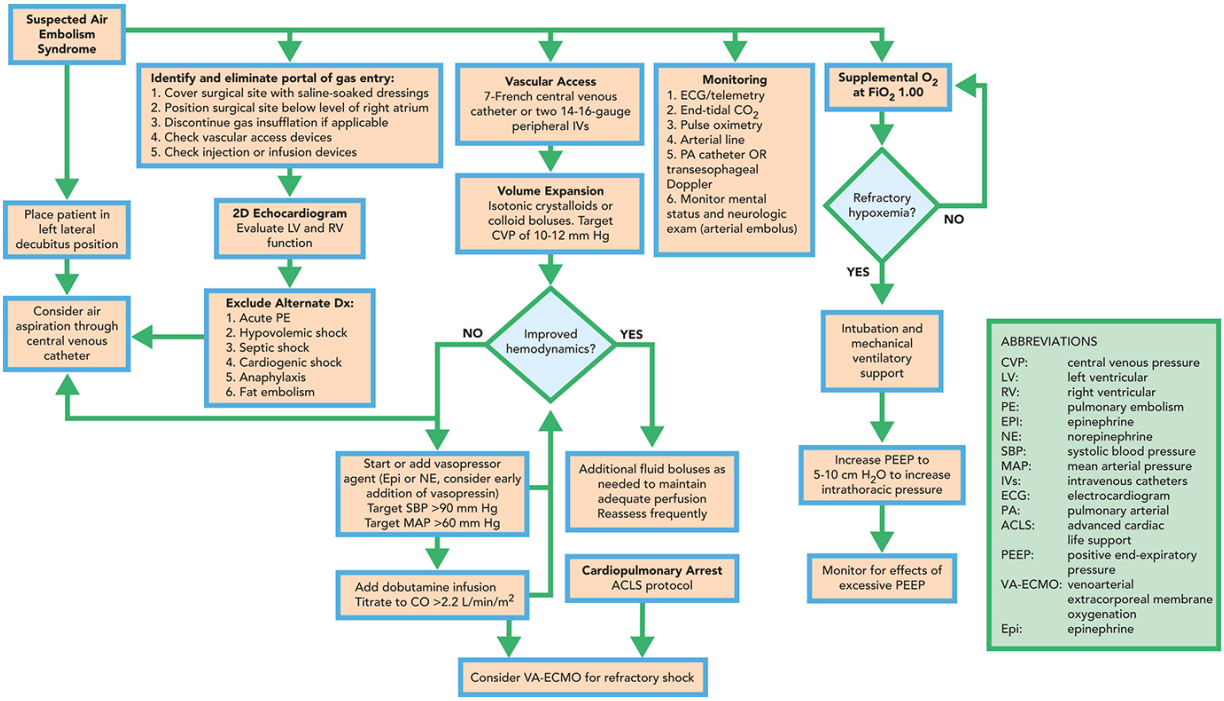
Gas enters the venous circulation when there is a negative intrathoracic pressure in the presence of an open central or peripheral vein, or if the open vein is elevated above the right atrium. Even a seemingly small pressure gradient of −5 cm H_2O is sufficient to allow gas to enter the venous circulation at up to 100 mL/s through a 14-gauge peripheral intravenous (IV) catheter. In the setting of volume depletion and decreased central venous pressure, or if the extravascular environment is under positive pressure (e.g., CO_2 insufflation during laparoscopic surgery), the risk of venous gas embolism increases significantly. Animal studies have shown that sudden, large-volume gas embolism is lethal. On the other hand, slow, continuous small-volume gas embolism is survivable, even if the cumulative volume of gas is large. In humans, the estimated lethal dose in venous AES is approximately 200 to 300 mL, and up to 500 mL if gas is entrained slowly. However, acute embolism of as little as 50 mL of gas may be sufficient to cause hemodynamic compromise.

Venous AES produces mechanical shock mainly through obstruction of the RV outflow tract. The severity of hemodynamic and gas exchange abnormalities depends on (1) total volume of gas entrained, (2) the rate at which gas enters the pulmonary arterial circulation, (3) preexisting CPD, and (4) severity of the inflammatory response triggered by the gas deposited in the pulmonary circulation. Unlike embolism of solid materials such as thrombus or fat, gas entering the pulmonary arterial circulation is eliminated continuously by diffusion across alveolar capillaries. Thus, if the portal of gas entry is eliminated, and if RV performance is capable of compensating for the elevated PVR, AES-induced mechanical shock should resolve as the embolized gas is cleared.

AES should be considered in the differential diagnosis for patients presenting with acute hemodynamic instability and gas exchange abnormalities in the proper clinical setting. Table 6.1 lists common

risk factors for AES. Mechanical shock induced by AES may be difficult to distinguish from other etiologies of shock. If arterial air embolism occurs and air enters the coronary arterial circulation, cardiogenic shock is added to the picture. Early assessment of hemodynamic function using 2D echocardiography, transesophageal Doppler, or pulmonary artery (PA) catheter can determine the predominant cause of shock. Therapy for AES is supportive and should focus on (1) eliminating the portal of gas entry, (2) restoring hemodynamic stability, and (3) promoting clearance of the entrained gas. A management algorithm for AES is shown in Algorithm 6.3.

ALGORITHM 6.3 **Management Algorithm for Air Embolism Syndrome**


Suspected Air Embolism Syndrome
Identify and eliminate portal of gas entry:
1. Cover surgical site with saline-soaked dressings
2. Position surgical site below level of right atrium
3. Discontinue gas insufflation if applicable
4. Check vascular access devices
5. Check injection or infusion devices
Vascular Access
7-French central venous catheter or two 14-16-gauge peripheral IVs
Monitoring
1. ECG/telemetry
2. End-tidal CO_2
3. Pulse oximetry
4. Arterial line
5. PA catheter OR transesophageal Doppler
6. Monitor mental status and neurologic exam (arterial embolus)
Supplemental O_2 at FiO_2 1.00
Place patient in left lateral decubitus position
2D Echocardiogram
Evaluate LV and RV function
Volume Expansion
Isotonic crystalloids or colloid boluses. Target CVP of 10-12 mm Hg
Refractory hypoxemia?
NO
YES
Consider air aspiration through central venous catheter
Exclude Alternate Dx:
1. Acute PE
2. Hypovolemic shock
3. Septic shock
4. Cardiogenic shock
5. Anaphylaxis
6. Fat embolism
Improved hemodynamics?
NO
YES
Intubation and mechanical ventilatory support
Start or add vasopressor agent (Epi or NE, consider early addition of vasopressin)
Target SBP >90 mm Hg
Target MAP >60 mm Hg
Additional fluid boluses as needed to maintain adequate perfusion
Reassess frequently
Increase PEEP to 5-10 cm H_2O to increase intrathoracic pressure
Add dobutamine infusion
Titrate to CO >2.2 L/min/m^2
Cardiopulmonary Arrest
ACLS protocol
Monitor for effects of excessive PEEP
Consider VA-ECMO for refractory shock
ABBREVIATIONS
CVP: central venous pressure
LV: left ventricular
RV: right ventricular
PE: pulmonary embolism
EPI: epinephrine
NE: norepinephrine
SBP: systolic blood pressure
MAP: mean arterial pressure
IVs: intravenous catheters
ECG: electrocardiogram
PA: pulmonary arterial
ACLS: advanced cardiac life support
PEEP: positive end-expiratory pressure
VA-ECMO: venoarterial extracorporeal membrane oxygenation
Epi: epinephrine

Although there are no randomized clinical trial data, air aspiration from the RV through a central venous catheter has been reported to remove up to 50% of the embolized gas, producing rapid hemodynamic improvement. The patient is placed in the left lateral decubitus position, elevating the RV above its outflow tract and promoting migration of entrained air back into the RV. A central

venous catheter is then placed with the tip approximately 2 cm below the superior vena cava/right atrial junction, and air is aspirated through the distal port. In the setting of refractory cardiopulmonary arrest, emergency thoracotomy, cardiac massage, and direct aspiration of air through the RV may be attempted as a last resort.

Emphasis should be placed on prevention of gas embolization during surgical and medical procedures through adequate hydration, proper patient positioning, avoidance of barotrauma, and observing proper procedures for vascular access insertion and removal. Patients at high risk for AES should be closely monitored via capnography or precordial Doppler ultrasound to detect gas embolization during surgical procedures. Early detection and prompt supportive treatment of AES can dramatically improve outcomes.

Fat Embolism

Fat embolism syndrome (FES) occurs when fat from necrotic bone marrow or adipocytes is released into the venous circulation following trauma or tissue injury, causing mechanical obstruction of the pulmonary vascular bed and triggering a systemic inflammatory response. Approximately 90% of cases of FES occur following blunt trauma, resulting in pelvic and long bone fractures. The risk of developing FES rises with the severity of the injury and the number of large marrow−containing bones involved.

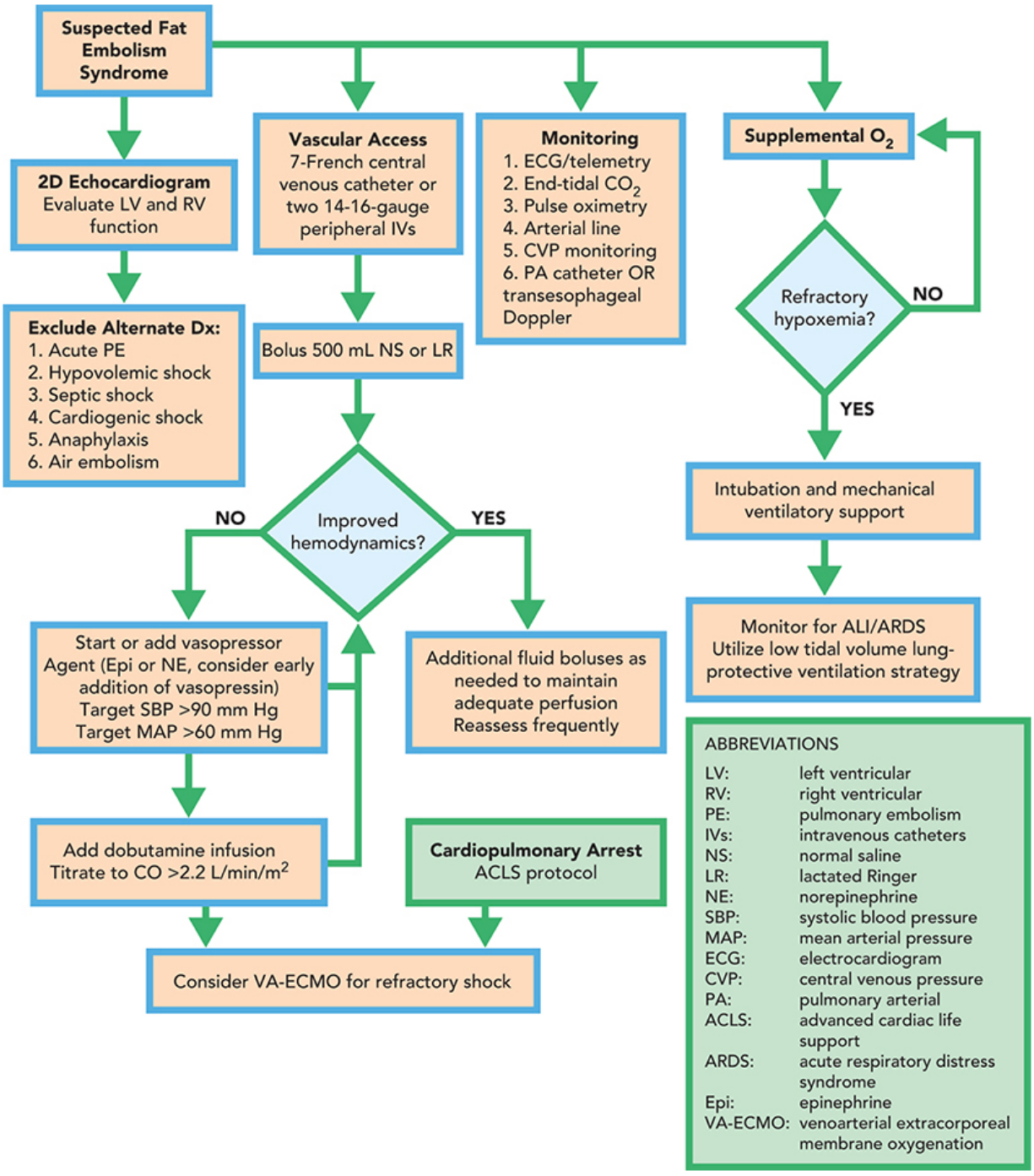
The pathobiology of FES remains incompletely understood. Studies have shown circulating fat in blood specimens collected from patients undergoing orthopedic surgery. This observation suggests the presence of fat in the circulation is necessary but not sufficient to precipitate FES. The severity of FES-induced mechanical shock probably depends on multiple factors, including (1) the total volume and rate of fat embolization, (2) immunogenicity of the embolized material, (3) intensity of the host inflammatory response, and (4) preexisting CPD.

Shock in the early phase of FES is mainly caused by mechanical obstruction of the pulmonary vasculature causing RV failure. Within

24 to 72 hours of the initial insult, toxic-free fatty acid metabolites cause systemic inflammation, acute lung injury, and end-organ dysfunction, with hemodynamic derangements similar to those found in septic shock. A classic triad of clinical findings consisting of hypoxemia, neurologic dysfunction, and petechial rash involving the upper trunk and axilla may be found in some patients.

No specific diagnostic test is available for FES. Treatment is supportive and should be focused on (1) restoring hemodynamic stability and (2) maintaining adequate oxygenation to avoid end-organ dysfunction. There is some evidence for prophylactic administration of corticosteroids in patients at high risk for FES. However, there is no evidence to support corticosteroid use after the FES has occurred. A management algorithm for FES is shown in Algorithm 6.4. A high clinical index of suspicion and early institution of supportive care are necessary to improve outcomes for patients with FES.

ALGORITHM 6.4 **Management Algorithm for Fat Embolism Syndrome**



Amniotic Fluid Embolism

Amniotic fluid embolism syndrome (AFES) occurs when AF enters the maternal circulation during labor and delivery or in the postpartum period due to cervical, uterine wall, or placental

membrane disruption. Classic findings include the acute onset of shock, hypoxemia, encephalopathy, coagulopathy, and disseminated intravascular coagulation. A fulminant presentation of AES can lead to circulatory collapse and death within a matter of hours. Survivors of this devastating syndrome are frequently left with severe neurologic impairment.

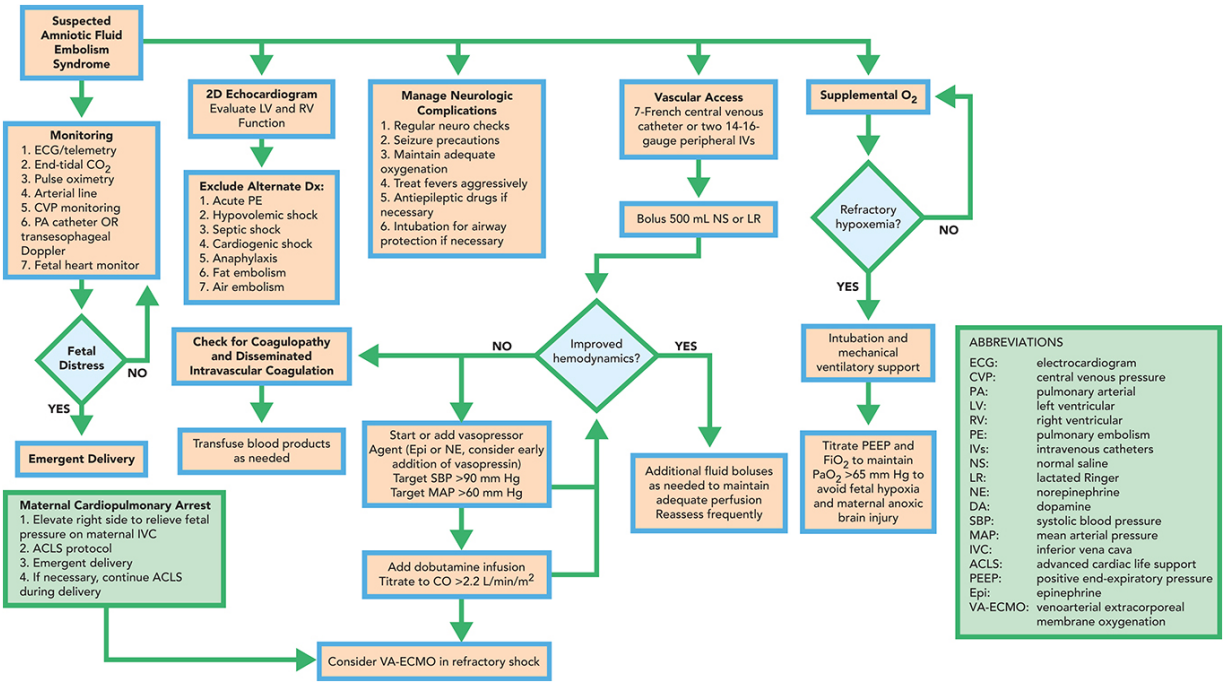
The pathogenesis of AFES remains incompletely understood. AF contains a heterogeneous mixture of water, electrolytes, hormones, and fetal components. AF components are routinely found in blood specimens from asymptomatic pregnant women, suggesting that entry of AF components into the maternal circulation is necessary but not sufficient to cause AFES. The development of AFES is likely determined by multiple factors, including (1) absolute volume of AF and its rate of entry into the maternal circulation, (2) AF composition, which affects its immunogenicity and vasoactive properties, (3) maternal immune response, and (4) preexisting maternal CPD.

The etiology of AFES-induced shock is often multifactorial and temporally heterogeneous. The early phase of AFES is dominated by severe acute left ventricular (LV) systolic dysfunction and cardiogenic shock. This may be accompanied by arrhythmias including bradycardia, ventricular fibrillation, pulseless electrical activity, or even asystole. Deposition of AF in the pulmonary circulation triggers intense pulmonary vasoconstriction, RV failure, and precipitates mechanical shock. The late phase of AFES, typically occurring 1 to 2 hours later, is frequently complicated by distributive shock caused by the severe systemic inflammatory response triggered by immunogenic AF components. Cardiogenic and obstructive shock may persist into the late phase of AFES, but usually improve over time. Disseminated intravascular coagulation and coagulopathy may add hemorrhagic shock to the picture.

The acute onset of agitation, altered mental status, dyspnea, and hemodynamic instability in a pregnant or peripartum woman should raise clinical suspicion for AFES. No specific diagnostic test is available for diagnosing AFES. Management of AFES is supportive and consists of the following goals: (1) restoring and maintaining maternal hemodynamic stability, (2) maintaining adequate

oxygenation to prevent maternal and fetal hypoxia, (3) correcting anemia and coagulopathy, (4) treating neurologic manifestations, and (5) expediting delivery of the fetus. A management algorithm for AFES is shown in Algorithm 6.5.

ALGORITHM 6.5 **Management Algorithm for Amniotic Fluid Embolism Syndrome**



Bedside 2D echocardiography is a useful modality for rapidly assessing LV and RV function. As multiple etiologies of shock are commonly encountered during the course of AFES, a transesophageal Doppler or PA catheter is useful for monitoring changing hemodynamic status and for guiding fluid resuscitation and titration of vasopressors and inotropes. Successful management of AFES requires early recognition, prompt initiation of supportive measures, and close coordination between the intensivist, obstetrician, and anesthesiologist.

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7 Emergency Department as the Gateway to the Intensive Care Unit

Brian M. Fuller and Julianne Yeary

Annually in the United States, emergency departments (EDs) care for almost 150 million patient visits, indicating that the ED is the safety net for the health care system. These patient volumes are increasing, with the most rapid increase for higher acuity and critically ill patients, and the ED cares for more than 5 million critically ill patients annually. In addition, the number of available in-hospital beds has fallen and more EDs are closing each year. Consequently, boarding of critically ill patients in the ED (prolonged treatment of patients in the ED after inpatient admission secondary to a lack of inpatient beds) is commonplace, lasts hours and even days, and is negatively associated with patient-centered outcomes, including mortality.

These figures demonstrate that the ED is the safety net not only for the health care system but also for the intensive care unit (ICU). Historical experience has demonstrated that time-sensitive interventions in the ED can prevent morbidity and mortality in deadly disease states such as sepsis, stroke, trauma, and acute myocardial infarction. In addition, interventions applied for critically ill patients in the ED not only modify outcome but influence trajectory and treatment decisions beyond ED discharge and into the ICU (ie, “therapeutic momentum”). This chapter will discuss important findings related to the initial (ie, ED) management of modifiable variables in two vulnerable patient cohorts: (1) mechanically ventilated patients and (2) patients with vasopressor-dependent shock.

Mechanically Ventilated Emergency Department Patients

MANAGEMENT OF MECHANICAL VENTILATOR SETTINGS

More than 350,000 patients require mechanical ventilation in the ED annually in the United States, and this is increasing; more than 30% of them will die. Even if patients survive, the rate of subsequent disability can be staggering, as survivors often suffer long-term sequelae, including posttraumatic stress disorder (PTSD), depression, anxiety, and impaired quality of life.

The optimization of ventilator settings in the ED could be especially impactful for several reasons. First, there is strong biologic rationale to target the postintubation phase of care in the ED with respect to optimization of ventilator settings. Animal data, which are supported by human data from the operating room, demonstrated that mechanical ventilation can promote lung injury, inflammation, and organ dysfunction in minutes to hours. Second, clinical data in the critically ill subsequently showed that a lung-protective ventilator strategy improves outcome in patients with acute respiratory distress syndrome (ARDS), with increased recognition of benefit in patients without ARDS as well. Third, ventilator settings in the early phase of respiratory failure are particularly impactful on outcome in patients with ARDS and those at risk. This is especially critical when considering that initial ventilator settings typically persist and change very little over the course of the first several days of care, an embodiment of therapeutic momentum initiated in the ED.

There is a growing body of evidence that demonstrates the influence of ED ventilator settings on patient-centered outcomes as well. Initial data from the ED domain, in single- and multicenter studies, demonstrated: (1) the frequent use of high tidal volume (eg, 8.8 mL/kg [7.8-10.0] predicted body weight [PBW]); (2) the presence of ARDS in a significant proportion of ED patients or within 2 days of ICU admission; and (3) that how the ventilator was set in the ED influenced early ICU settings. An ensuing before-after clinical trial (*n*

= 1,705 patients) demonstrated that an ED-based default lung-protective approach improved adherence to lung protection in both the ED and ICU and was associated with improved clinical outcomes. A secondary analysis, which spanned approximately a decade, of individual patient-level data (*n* = 3,199 patients) from prior clinical trials and cohort studies showed that this default, ED-based lung-protective approach was sustainable with: (1) tidal volume reduction from 8.2 to 6.5 mL/kg PBW over the time period; and (2) lower mortality and more ventilator-free days. Finally, a comprehensive systematic review and meta-analysis that included 11 studies (*n* = 12,912 patients) demonstrated that ED low tidal volume ventilation was associated with lower mortality (26.5%) versus non−low tidal volume ventilation (31.1%) (odds ratio, 0.80 [0.72-0.88]), more ventilator-free days, and shorter stays in the ICU and hospital.

In summary, the growing body of evidence demonstrates that ED-based lung-protective ventilation is associated with the improved delivery of mechanical ventilation throughout a patient's course and better clinical outcomes. However, it should be stressed that a "one-size-fits-all" approach should not be employed for all patients on a mechanical ventilator. The data suggest that a lung-protective approach in the ED should be the default, overarching approach to initial settings in the ED, but settings at the patient level should be tailored to the individual's physiology and clinical status in a short-loop feedback manner. Recognizing this, Table 7.1 provides a simple and general guideline to initial ED ventilator settings.

TABLE 7.1 **Guidelines for Initial Ventilator Settings in the Emergency Department**

Clinical Strategy

	Default Approach: Lung-Protective Ventilator Strategy	Auto-PEEP Strategy	Severe Metabolic Acidosis Strategy
Patient cohort example	Hypoxemia (eg, ARDS) and great majority of all patients in the ED	Status asthmaticus, acute exacerbation of COPD	DKA, salicylate toxicity
Mode	Volume control assist (VC-AC)	Volume control assist (VC-AC)	Volume control assist (VC-AC)
Tidal volume	6-8 mL/kg PBW • Closer to 6 mL/kg PBW if ARDS present in ED	8-10 mL/kg PBW	8-10 mL/kg PBW
PEEP	≥5 cm H_2O • Estimated BMI > 30, set PEEP to 8 cm H_2O; estimated BMI > 40, set PEEP to 10 cm H_2O • For simplicity, use ARDSNet PEEP-F_{IO_2} table	≥5 cm H_2O • Applied at a level to overcome auto-PEEP when patient is triggering ventilator	≥5 cm H_2O • Can apply similar principles as the default approach

FiO_2	Start at 30%-40% • Titrate for SpO_2 90%-95% or PaO_2 ~60 mm Hg • Titrate up in combination with PEEP increase	Start at 30%-40% • Titrate for SpO_2 ≥88% or PaO_2 ~55 mm Hg	Start at 30%-40% • Titrate for SpO_2 90%-95% or PaO_2 ~60 mm Hg • Titrate up in combination with PEEP increase
Respiratory rate	20-30 breaths/min • Monitor for auto-PEEP	8-10 breaths/min • Set low to allow adequate expiratory time • Allow permissive hypercapnia (do not try and normalize arterial blood gas values)	Set high • Try to match preintubation minute ventilation • If $PaCO_2$ is known, a rough guide for initial minute ventilation is: • Goal minute ventilation = ($PaCO_2$ × minute ventilation [set on vent])/(goal $PaCO_2$ [Winter Equation])

Critical monitoring	Plateau pressure • Goal <30 cm H_2O; in patients with reduced chest wall compliance (eg, obesity, ascites) can accept higher plateau • Checked with inspiratory hold maneuver	Auto-PEEP • If flow/time waveform does not return to zero, auto-PEEP is present • Can quantify with expiratory hold maneuver	$Paco_2$, $Etco_2$ • Use Winter formula for goal $Paco_2$
Notes	In general, ED providers set PEEP typically too low for hypoxemic patients in the ED.	If rate needs to be exceptionally low due to auto-PEEP, tidal volume will likely need to be increased to avoid life-threatening acidosis. The risks of acidosis and auto-PEEP must be balanced in the most severely ill.	Can revert to default approach as metabolic acidosis resolves

ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DKA, diabetic ketoacidosis; ED, emergency department; $EtCO_2$, end tidal carbon dioxide; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SpO_2, peripheral oxygen saturation.

EMERGENCY DEPARTMENT MANAGEMENT OF SEDATION

The management of sedation is a cornerstone therapy for mechanically ventilated patients and is highly influential on outcome. Owing to more than 20 years of published research and increasingly

evidence-based guidelines, important recommendations exist, which are associated with improved patient-centered outcomes. These include the use of sedation protocols, daily sedation interruptions, and targeting light sedation unless clinically indicated otherwise. However, similar to the management of mechanical ventilation, these data have historically focused solely on the ICU phase of therapy and ignored the critical time spent in the ED.

There is strong biologic rationale to avoid deep sedation by targeting the ED, as deep sedation has negative pleiotropic effects on many organ systems (including the profound effects on the brain), including the gastrointestinal (GI) tract and immune system. Clinical consequences of deep sedation include a higher incidence of ventilator-associated pneumonia, GI dysfunction, and deep venous thrombosis. Relevant to the ED, these clinical sequelae occur early, within 1 to 2 days of ICU admission. These sequelae translate into patient-oriented outcomes, as deep sedation has been linked to greater mortality, mechanical ventilation duration, lengths of stay, and negative mental health outcomes.

Similar to mechanical ventilation, there is a growing body of evidence that shows the critical importance that the ED can play with respect to sedation management. Initial ED-based data demonstrated an incidence of deep sedation (ie, Richmond Agitation Sedation Scale [RASS] −3 to −5) of 64%, and an association between deep sedation and increased mortality and longer mechanical ventilation duration. Similar findings were demonstrated in a multicenter (n = 15) ED study and a comprehensive systematic review and meta-analysis, which demonstrated that early light sedation, compared to deep sedation, was associated with lower mortality, less delirium, and shorter ventilator duration. These studies also demonstrated that deep sedation in the ED persisted into the first 2 days of ICU care, another example of therapeutic momentum generated during the earliest period of critical illness. To plan for an adequately powered clinical trial, the ED-SED Pilot Trial was undertaken to demonstrate if a targeted, ED-based default light sedation strategy was feasible. In this trial, an education-based intervention resulted in: (1) an increase in sedation assessments in

the ED; (2) the achievement of lighter sedation levels in the ED with a reduction in the proportion of patients experiencing deep sedation reduced from 60.2% to 38.8%; and (3) no concerning trends in safety events (ie, inadvertent extubation, device removal, awareness with paralysis). Though not powered for clinical outcomes, the intervention was also associated with improved patient-centered outcomes.

In summary, ED-based sedation is influential on sedation levels during the first 2 days of ICU care. In addition, a protocol-driven default light sedation approach is feasible and holds promise for improved patient-centered outcomes.

Patients With Vasopressor-Dependent Shock

Similar to mechanically ventilated patients, those requiring vasopressors in the ED are also managed with increasing frequency due to longer boarding times, especially for ICU level of care. Choosing the optimal vasopressor in the initial patient presentation is critical, and highly dependent on mechanism of action and patient physiology.

Currently, the available vasopressors in the United States include norepinephrine, epinephrine, vasopressin, phenylephrine, dopamine, and angiotensin II. Table 7.2 provides catecholamines and other receptor targets for vasopressor therapy and their potency at respective receptors. Catecholamines (alpha and beta receptors) can lead to downstream effects such as vasoconstriction in peripheral tissues (alpha 1) to positive inotropy (beta 1). Complications from excessive catecholamine agonism can lead to ischemia (alpha 1) and tachyarrhythmias (beta 1), which may warrant other vasopressors to minimize excessive catecholamine stimulation.

TABLE 7.2 **Vasopressor Receptor Targets and Their Potency at Respective Receptors**

	Receptor Targets						
	Alpha 1	Alpha 2	Beta 1	Beta 2	DA	VP	ATI
Norepinephrine	++++	++	++	–	–	–	–
Epinephrine (mcg/kg/min)							
0.01-0.05	++	++	++++	+++	–	–	–
>0.05	++++	++++	+++	+	–	–	–
Phenylephrine	++++	+	–	–	–	–	–
Dopamine (mcg/kg/min)							
1-3	–	–	+	–	++++	–	–
3-10	–/+	–	++++	++	++++	–	–
10-20	+++	–	++++	+	–	–	–
Vasopressin	–	–	–	–	–	+++	–
Angiotensin II	–	–	–	–	–	–	+++

Norepinephrine is a potent alpha 1 and beta 1 agonist exerting vasoconstriction and significant increase in mean arterial pressure (MAP). Epinephrine exerts its effects by a dose-dependent action on both beta and alpha receptors. Lower doses (<0.05 mcg/kg/min) of epinephrine result in beta 1 activity, leading to increased cardiac output (CO) and decreased systemic vascular resistance (SVR). Higher doses (>0.05 mcg/kg/min) of epinephrine result in additional alpha activity, leading to increase in MAP. Dopamine is also dose dependent; low dose (<5 mcg/kg/min) acts on dopamine receptors leading to vasodilation within renal vasculature. Beta receptors are activated at doses of 5 to 10 mcg/kg/min, and doses of 10 to 20

mcg/kg/min act on alpha receptors. Phenylephrine is a strict alpha agonist, increasing MAP. However, it can be associated with bradycardia especially in patients with poor cardiac function.

Vasopressors without direct action on catecholamines include vasopressin and angiotensin II. Vasopressin acts on multiple vasopressin receptors that are located in the peripheral vasculature causing vasoconstriction (V1 receptors) and kidneys leading to an antidiuretic effect (V2 receptors). Angiotensin II is an endogenous hormone released from the renal-angiotensin-aldosterone system (RAAS) that has many roles including, but not limited to, increase in sodium and H^+ reabsorption in the kidneys as well as peripheral vasoconstriction.

SEPTIC SHOCK

Norepinephrine is considered the first-line vasopressor with a strong recommendation by the Surviving Sepsis Campaign Guidelines. It has been shown to be the optimal vasopressor as compared to dopamine by Avni and colleagues with decreased mortality (relative risk [RR] 0.89; 95% CI 0.81-0.98) and lower risk of arrhythmias (RR 0.48; 95% CI 0.40-0.58). However, in a randomized controlled trial comparing norepinephrine to epinephrine, there was no difference in 90-day mortality (hazard ratio [HR] 0.88; 95% CI 0.63-1.25) or vasopressor-free days.

Vasopressin, based on the Surviving Sepsis Campaign Guidelines, is recommended for use in addition to norepinephrine for its catecholamine-sparing effect, seen by both the VANISH trial and VASST trial. The VANISH trial was a randomized trial of septic shock patients comparing the use of vasopressin versus norepinephrine and found no difference between the groups in 28-day mortality (30.9% vs 27.5%; RR 1.13 [95% CI 0.85-1.51]) and kidney injury (RR 0.89; 95% CI 0.72-1.11). However, it did find vasopressin had a reduced risk of renal replacement therapy (RRT) as compared to norepinephrine (RR 0.71; 95% CI 0.53-0.97). The VASST trial evaluated the addition of vasopressin to norepinephrine and found no improvement in 28-day mortality (39.3% vs 35.4%, $P = .26$) but

found patients with less severe shock (defined as receiving norepinephrine <15 mcg/min) had improved survival with the addition of vasopressin (26.5% vs 35.7%; *P* = .05). More recent systematic reviews of up to 10 randomized controlled trials have shown reduced mortality with the addition of vasopressin to norepinephrine (RR 0.91; 95% CI 0.83-0.99) without significant reduction in need for RRT (RR 0.79; 95% CI 0.57-1.10).

Angiotensin II is one of the newest vasopressors to the market for the treatment of septic shock. The ATHOS-3 trial evaluated angiotensin II in addition to other vasopressors in septic shock and found a catecholamine-sparing effect, but no difference in mortality (46% vs 54%; HR 0.78; 95% CI 0.57-1.07; *P* = .12). Adverse events of angiotensin II are limited to ischemia and possible venous thrombus embolism, and angiotensin II is thus not recommended for first-line therapy given limited evidence outside of adjunct use with other vasopressors. The Surviving Sepsis Campaign Guidelines have not commented on angiotensin II use in septic shock and continued literature is needed to guide its place in therapy.

POST-RETURN OF SPONTANEOUS CIRCULATION (ROSC) IN OUT-OF-HOSPITAL CARDIAC ARREST

Out-of-hospital cardiac arrest (OHCA) is common and associated with high mortality and survivor morbidity. The American Heart Association 2020 Advanced Cardiac Life Support (ACLS) guidelines recommend that post-ROSC MAP be greater than 65 mm Hg, but do not provide a recommendation for one vasopressor over the other. A single-center, retrospective study evaluated norepinephrine (*n* = 45) versus epinephrine (*n* = 42) use in patients post-ROSC. The primary outcome included patients meeting the following criteria in each group: experienced refractory shock (defined as need for second vasopressor), rearrested, or died. Patients in the epinephrine group met the primary outcome significantly more often than the norepinephrine group (50% vs 22.2%; *P* = .008). The leading attributor to meeting the primary outcome was related to higher rates of ED rearrest in the epinephrine group (33.3% vs 15.6%; *P* = .079)

as compared to other attributing factors. Risk factors such as age, illness severity, time from arrest to cardiopulmonary resuscitation (CPR), CPR duration, presenting cardiac rhythm, vasopressor dose, and receipt of other ACLS doses were similar among both groups.

Another retrospective review of the Sudden Death Expertise Center registry in France reviewed initial vasopressor of epinephrine (n = 285) versus norepinephrine (n = 481) use post-ROSC and associated outcomes of all-cause mortality during hospital stay. Patients in the epinephrine group had a higher all-cause mortality in the hospital stay compared to those in the norepinephrine group (83% vs 61%, $P < .001$). Of note, patients in the epinephrine group had more nonshockable initial rhythms, longer time from CPR to ROSC, and higher lactate as compared to the norepinephrine group in regard to baseline characteristics. Early recurrent cardiac arrest was also seen more often in the epinephrine group versus the norepinephrine group (7% vs 2%, $P < .001$).

With majority of cardiac arrest and OHCA data being in a retrospective manner, it is imperative to consider the many confounders when attributing treatment regimens to outcomes. However, along with septic shock data and depending on primary cause of OHCA, norepinephrine may be the more appropriate vasopressor of choice post-ROSC to minimize rearrest and in-hospital mortality until further data regarding causes can be found.

PERIPHERAL ADMINISTRATION OF VASOPRESSORS

All vasopressors have the recommendation to be given through a central venous catheter (CVC) given their increased risk of extravasation caused by vasoconstriction. However, placing a CVC is a time-sensitive and labor-intensive process, and is associated with infectious risk if not completed in a sterile environment. Therefore, the safety of peripheral administration of vasopressors is a common clinical question.

Evidence regarding this topic is scarce and limited to case series, case reports, and very few randomized controlled trials. Evidence regarding vasopressor use in peripheral lines was reviewed by

Loubani and colleagues in 2015. After extensive literature searches, they found 85 studies evaluating this topic, which included a total of 270 patients and 325 separate events of local tissue injury or vasopressor extravasation related to intravenous (IV) vasopressor therapy; 318 events were related to peripheral IV administration. Vasopressors associated with instances of local tissue complications included norepinephrine (80.5%), dopamine (9.3%), and vasopressin (6.9%). Of note, the average duration of vasopressor infusion before an extravasation event was 55.9 hours (±68.1) and the majority of events (75.4%) did not result in any tissue injury.

Factors to consider when administering vasopressors through a peripheral line include concentration of the vasopressor (lowest if possible), peripheral line access site (above the antecubital; avoid smaller vasculature such as hand/feet), IV gauge (18 gauge or larger), expected duration of vasopressor need (<12-24 hours), and clinical trajectory. If these factors are clinically challenging to adhere to, it may be prudent to provide CVC access to minimize local tissue extravasation to the patient.

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SECTION II

MANAGEMENT OF RESPIRATORY DISORDERS

8 An Approach to Respiratory Failure

John C. Grotberg and Bryan D. Kraft

Respiratory failure is a common indication for admission to the intensive care unit and is the final common pathway for a number of respiratory diseases of differing pathophysiology. A mechanism-based approach enables the clinician to identify the most likely cause for the respiratory failure and to treat appropriately. In general, patients with respiratory failure may be classified into four groups, depending on the component of the respiratory system that is involved.

- Hypercapnic respiratory failure is a consequence of ventilatory failure and is recognized by an elevated $Paco_2$ (>45 mm Hg at sea level). This pattern of respiratory failure can result from many differing etiologies and generally denotes failure of the respiratory pump mechanism (ie, CO_2 elimination), which can occur in a patient with normal lung function, or as a consequence of airway disease, parenchymal lung disease, pulmonary vascular disease, or neuromuscular disease.
- Hypoxemic respiratory failure is a consequence of gas exchange failure and is recognized by hypoxemia (Pao_2 <60 mm Hg), with or without widening of the alveolar-arterial oxygen gradient. Most patients with this form of respiratory failure have ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch or shunting as the predominant mechanism(s). Patients will commonly have a parenchymal lung abnormality seen on chest x-ray or computed tomography (CT); however, intracardiac and intrapulmonary shunts can also present in this manner with fairly normal chest imaging.

- Mixed hypoxemic and hypercapnic respiratory failure occurs with components of multiple pathophysiologic processes that lead to both hypoxemia and hypercapnia.
- Respiratory failure due to shock occurs when the metabolic demands of the body exceed the ability of the respiratory system to compensate. This is common in patients with sepsis or profound metabolic derangements like lactic acidosis.

Hypercapnic Respiratory Failure

The hallmark of hypercapnic respiratory failure is an elevated $Paco_2$ above 45 mm Hg and described by the modified alveolar ventilation equation (Equation 1):

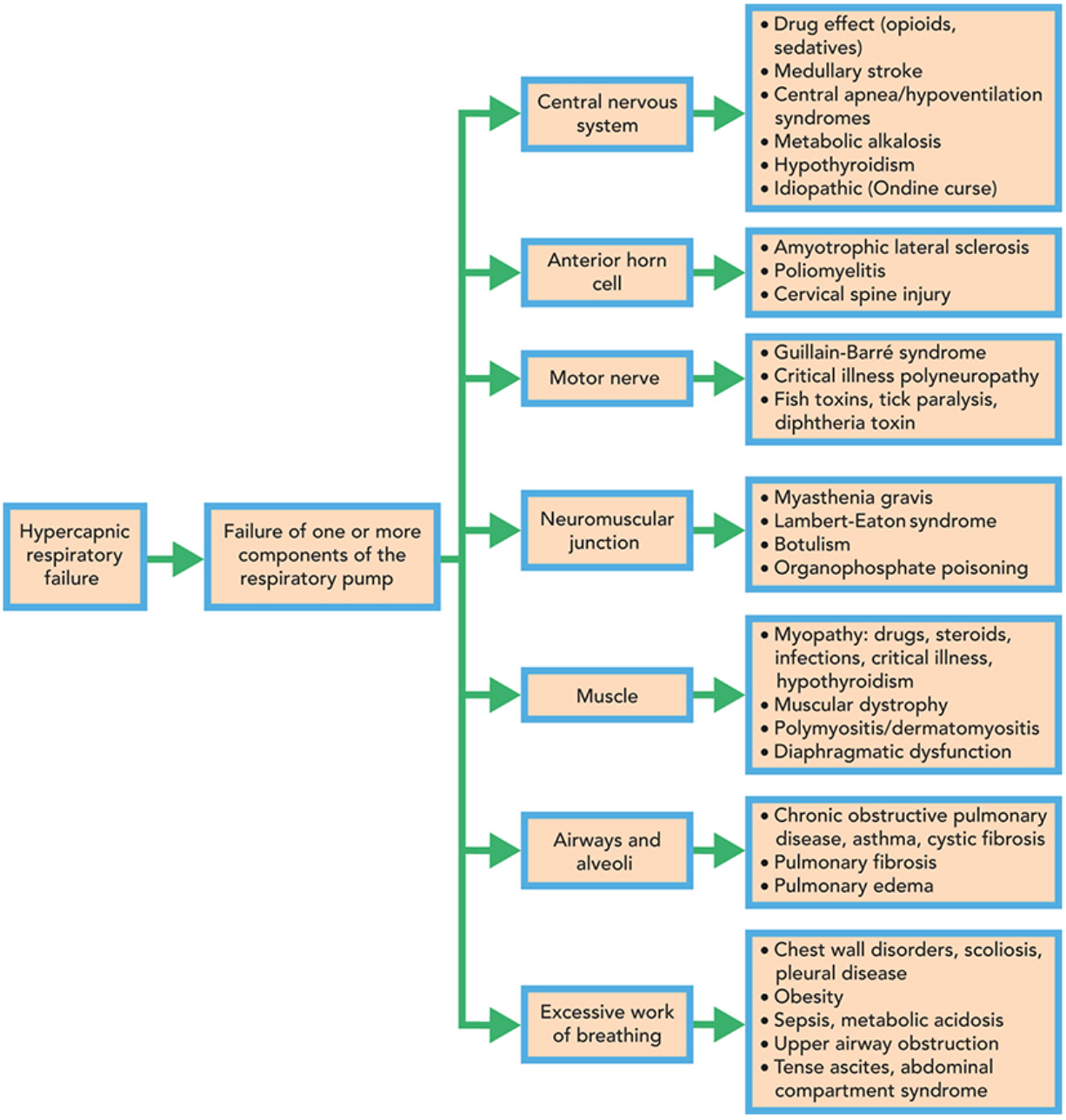
$$Paco_2 = k \times \frac{\dot{V}co_2}{\left(1 - \frac{V_d}{V_t}\right) \times V_E} \qquad (1)$$

where $Paco_2$ is the partial pressure of carbon dioxide in arterial blood, k constant, $\dot{V}\ co_2$ carbon dioxide production, V_d/V_t dead space ratio of each tidal volume breath, and V_E minute ventilation. It is important to note that the denominator is also equal to alveolar ventilation (V_A).

Equation 1 shows that hypercapnia can occur from three separate but related processes: (a) an increase in CO_2 production ($\dot{V}\ co_2$), which is the least common cause for hypercapnia; (b) a decrease in minute ventilation (V_E) by a reduced tidal volume, a reduced respiratory rate, or both; and (c) an increase in the dead space ratio (V_d/V_t, where V_d is the dead space volume and V_t is the tidal volume). It is not uncommon for two or more mechanisms to contribute to hypercapnia in critically ill patients with respiratory failure. Understanding the “respiratory pump” enables the clinician to

systematically consider the cause of hypercapnic respiratory failure in different patients, as depicted in Algorithm 8.1.

ALGORITHM 8.1 **Causes of Hypercapnic Respiratory Failure Based on Components of the Respiratory Pump**



The acuity of onset of the hypercapnia is also an important determinant of management. An acute change in $Paco_2$ of 10 mm Hg will change the blood pH by 0.08 in the opposite direction. In patients with chronic hypercapnia, renal compensation occurs by bicarbonate retention and mitigates the drop in pH but does not normalize it. In these cases, a change in $Paco_2$ of 10 mm Hg is reflected by a change of 0.03 in the blood pH in the opposite direction.

Important principles in managing patients with hypercapnia are:

- Rapidly institute adequate ventilation: In carefully selected patients, noninvasive ventilation can be initiated prior to intubation and mechanical ventilation. The goal of improving ventilation is to bring the pH to a safe level rather than to normalize the Pco_2.
- Cautious use of supplemental oxygen is necessary as oxygen can worsen hypercapnia by a number of mechanisms: worsening of $\dot{V}/\dot{Q}$ matching, the Haldane effect, and suppression of central hypoxemic drive. Enough supplemental oxygen should be given to maintain the oxyhemoglobin saturation in the 88% to 92% range in most patients with hypercapnia with underlying severe obstructive lung disease.
- Sedatives and narcotics can be hazardous and can worsen ventilation and oxygenation in patients with hypercapnia, particularly those with neuromuscular weakness and severe obstructive lung disease.

Hypoxemic Respiratory Failure

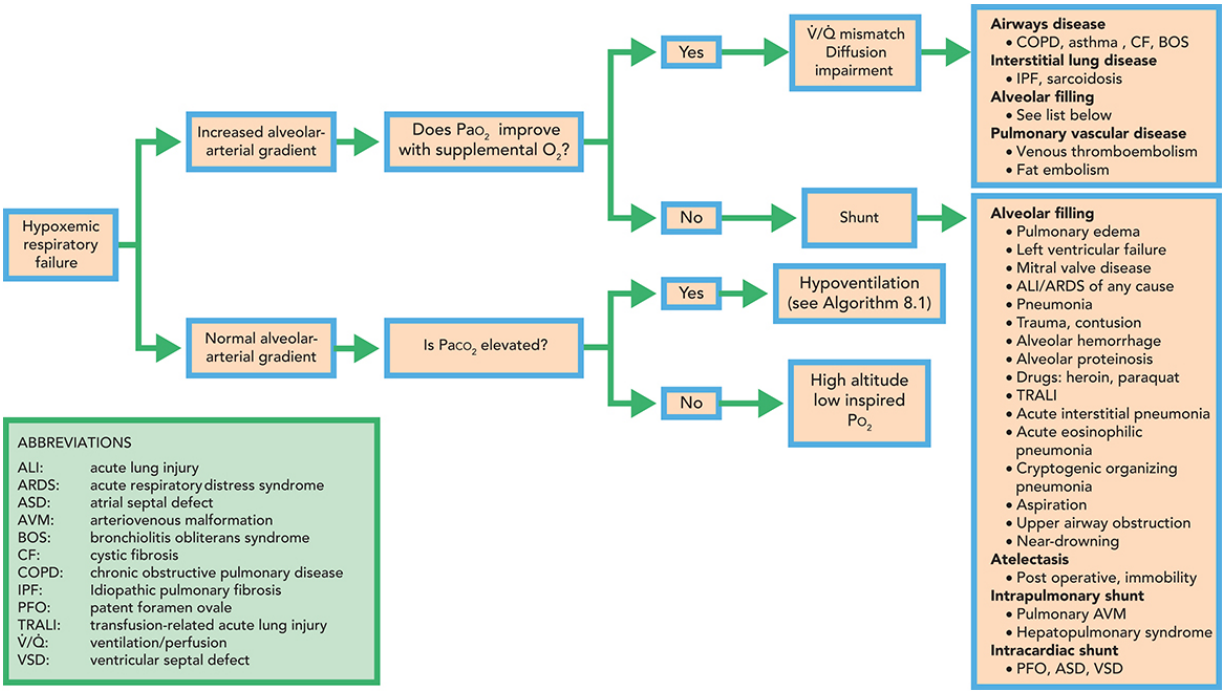
Hypoxemic respiratory failure occurs because of impaired gas exchange or hypoventilation and is defined by a Pao_2 of <60 mm Hg. The first step in ascertaining a cause for hypoxemia is calculating the alveolar-arterial oxygen gradient by using the alveolar gas equation

(Equation 2). The approach to hypoxemic respiratory failure is summarized in Algorithm 8.2.

$$P_{AO_2} = F_{IO_2}\,(PB - PH_2O) - \frac{Paco_2}{R} \qquad (2)$$

where P_{AO_2} is the alveolar partial pressure of oxygen, F_{IO_2} fraction of inspired oxygen, PB barometric pressure (760 mm Hg at sea level), P_{H_2O} water vapor pressure (47 mm Hg), $Paco_2$ partial pressure of carbon dioxide in arterial blood, and *R* respiratory quotient, assumed to be 0.8.

ALGORITHM 8.2 **General Approach to Hypoxemic Respiratory Failure**



The alveolar-arterial oxygen gradient = $P_{AO_2} - Pa_{O_2}$. The normal value is between 10 and 15 mm Hg and is influenced by age, increasing by approximately 3 mm Hg for every decade after the age of 30 years. For an F_{IO_2} = 0.21, it should be 5 to 25 mm Hg, and for

an F_{IO_2} = 1.0, it should be <150 mm Hg. Hypoxemic respiratory failure with a widened alveolar-arterial oxygen gradient is caused by $\dot{V}/\dot{Q}$ mismatching, shunt pathophysiology, or diffusion impairment. Hypoxemia due to $\dot{V}/\dot{Q}$ mismatch or diffusion impairment will correct with supplemental oxygen, whereas no (or minimal) improvement is seen in cases purely due to shunt. Common causes of hypoxemic respiratory failure include airspace flooding (eg, pulmonary edema, pneumonia), atelectasis, airway disease, or pulmonary vascular disease.

Management principles for patients with hypoxemic respiratory failure include:

- rapid restoration of an adequate arterial saturation, which may require intubation and mechanical ventilation or simply provision of supplemental oxygen. Patients with hypoxemia and pulmonary infiltrates not due to atelectasis or cardiogenic pulmonary edema generally respond less well to noninvasive ventilation, but may do quite well on heated, humidified high-flow nasal oxygen.
- use of adequate amounts of positive end-expiratory pressure to reduce F_{IO_2} to nontoxic levels (F_{IO_2} <60%).
- a low tidal volume strategy with permissive hypercapnia in patients with acute respiratory distress syndrome.
- general supportive care in the intensive care unit while the patient's pulmonary process resolves.

In contrast to hypoxemia, hypoxia refers to an oxygen deficit at a tissue level and depends on oxygen delivery. Therefore, cellular hypoxia can be a result of any process that affects oxygen delivery to the tissues and includes:

- hypoxemic hypoxia (low arterial oxygen saturation and a low Pa_{O_2}).
- anemic hypoxia (low-circulating hemoglobin with impaired oxygen delivery).
- circulatory hypoxia (low cardiac output states).

- cytopathic hypoxia (disruption of the electron transport chain and oxidative phosphorylation, for instance from cyanide poisoning or mitochondrial injury).

The determinants of oxygen delivery (DO_2) include the cardiac output, the hemoglobin concentration, and the oxygen saturation of hemoglobin (Equation 3). Some critically ill patients in the intensive care unit have an increase in oxygen consumption ($\dot{V}O_2$), particularly those with fever, pain, inflammation, respiratory distress, and increased catecholamines. Some patients may exhibit a reduced $\dot{V}O_2$, particularly those with multiple organ failure or those receiving neuromuscular blockade. When the ratio of oxygen delivery to oxygen consumption exceeds a critical threshold, cellular mechanisms shift to anaerobic metabolism resulting in the generation of lactate (Figure 8.1). Though cardiac output is often the largest contributor to oxygen delivery, it is not uncommon for patients to have more than one factor contributing to cellular hypoxia. For example, a patient with pneumonia, anemia, and septic shock may have hypoxemic hypoxia, anemic hypoxia, circulatory hypoxia, and cytopathic hypoxia secondary to mitochondrial dysfunction.

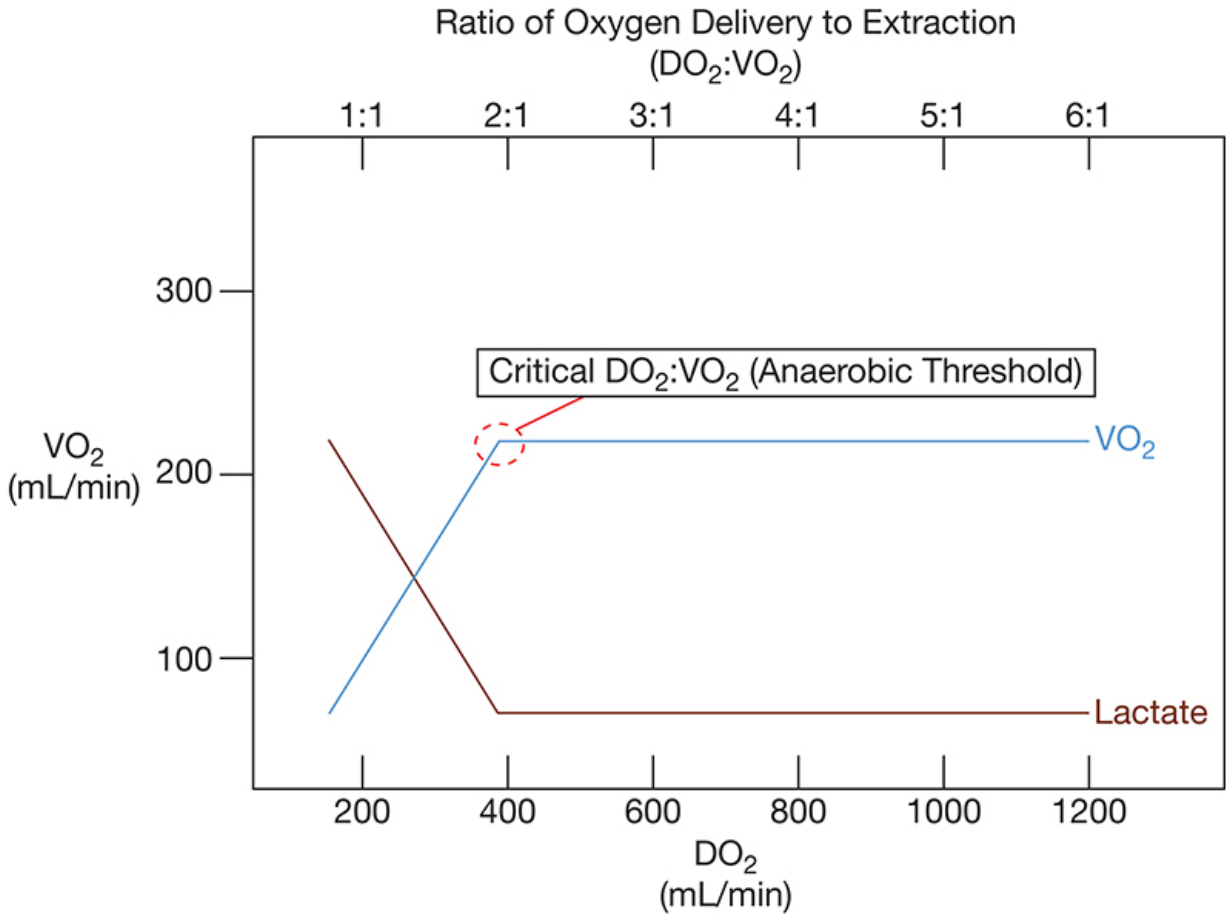


FIGURE 8.1 **The relationship between oxygen delivery and oxygen consumption.** A schematic demonstrating the relationship between oxygen delivery (Do_2) and oxygen consumption ($\dot{V}o_2$). As the ratio of Do_2:$\dot{V}o_2$ decreases, a critical threshold is reached where anaerobic metabolism predominates and lactate levels rise.

$$\text{Oxygen Delivery} = \text{Cardiac Output} \times \text{Arterial Oxygen Content}$$

$$Do_2 = CO \times Cao_2$$

$$Do_2 = CO \times (1.39\ [Hb\ (g/dL)] \times Sao_2) + (0.003 \times Pao_2) \quad (3)$$

Monitoring Oxygenation and Ventilation

The partial pressure of carbon dioxide at the end of exhaled breath is called end-tidal CO_2 ($ETCO_2$) and represents the alveolar partial pressure of CO_2. As a surrogate for ventilation, $ETCO_2$ can be monitored continuously in mechanically ventilated patients using quantitative waveform capnography. Both the $ETCO_2$ and capnogram shape provide useful information when monitoring ventilation in a patient with hypercapnic respiratory failure. The $ETCO_2$ waveform can be divided into four phases (Figure 8.2A): (a) phase 0 represents inspiration; (b) phase I represents anatomic dead space; (c) phase II represents a mixture of anatomic dead space and alveolar gas; and (d) phase III represents pure alveolar gas. The difference between the $PaCO_2$ and the $PETCO_2$, known as the $P_{a\text{-}ET}CO_2$, is normally approximately 5 mm Hg. This close approximation (in most patients) allows the use of continuous $ETCO_2$ to monitor quantitative changes in CO_2, providing the clinician with vital information regarding CO_2 elimination and ventilation of the patient. An increase in the $P_{a\text{-}ET}CO_2$, however, may reflect increasing alveolar dead space ventilation (Figure 8.2B), which can inform the clinician of alterations in the patient's respiratory status. The ratio of dead space volume to tidal volume, or the dead space ratio (V_d/V_t), can be readily estimated at the bedside using the $PaCO_2$ and the mixed expired CO_2 ($PeCO_2$), which reflects the partial pressure of CO_2 in the alveoli and conducting airways (phases II and III on the capnogram, Figure 8.2B). This is accomplished with the modified Bohr equation (Equation 4).

$$\frac{V_d}{V_t} = \frac{PaCO_2 - PeCO_2}{PaCO_2} \qquad (4)$$

Where V_d is the volume of exhaled breath arising from physiologic dead space, V_t tidal volume, $PaCO_2$ partial pressure of arterial carbon dioxide (mm Hg), and $PeCO_2$ partial pressure of mixed expired CO_2 (mm Hg).

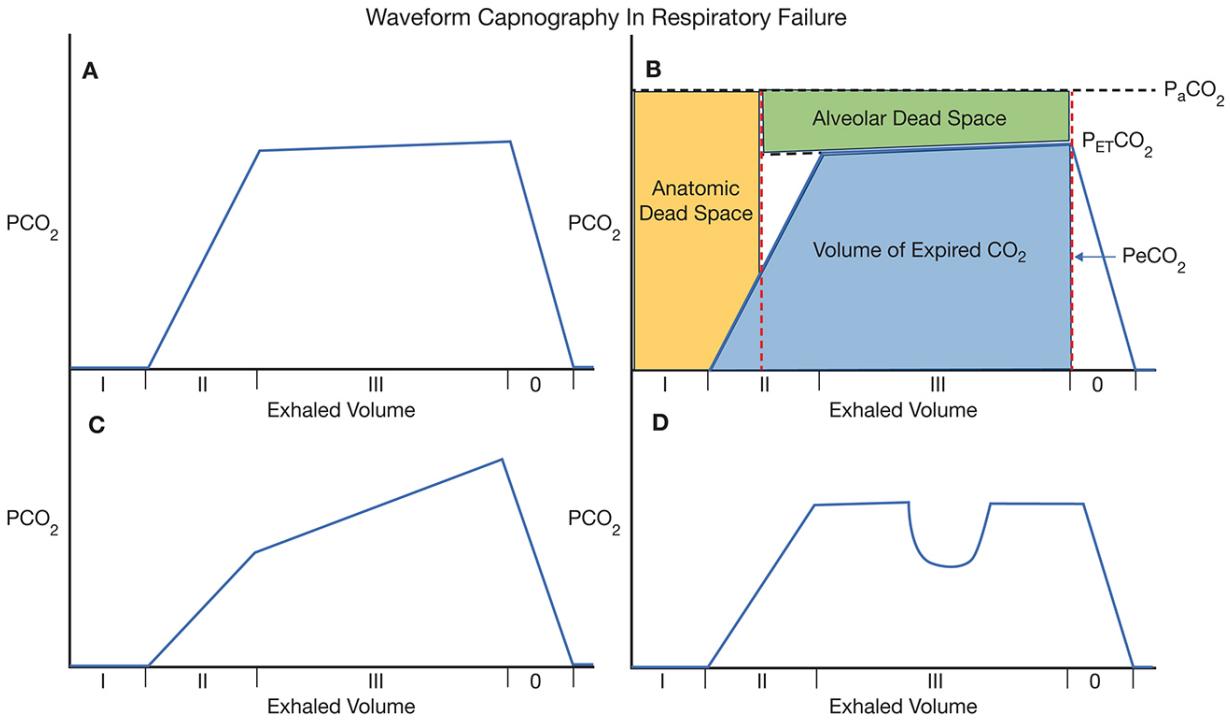


FIGURE 8.2 **Waveform capnography in respiratory failure.** A schematic demonstrating quantitative waveform capnography by measuring the end-tidal CO_2 ($ETco_2$) where Pco_2 is the partial pressure of carbon dioxide, $Paco_2$ is the arterial partial pressure of carbon dioxide, $Petco_2$ is the end-tidal partial pressure of carbon dioxide, and $Peco_2$ is the mixed expired partial pressure of CO_2 in the alveoli and conducting airways. Panels in the schematic represent the following: **A:** a normal capnogram, **B:** the relationship between the $Paco_2$ and $Petco_2$ gradient and dead space ventilation, **C:** a capnogram in acute obstructive lung disease, **D:** a capnogram with a "curare cleft" representing ventilator asynchrony in a mechanically ventilated patient.

The shape of the capnogram can also provide useful information. For example, patients with acute exacerbations of obstructive lung disease (eg, asthma/chronic obstructive pulmonary disease [COPD]) may exhibit a prolonged phase II and phase III with an increased slope of phase III in the setting of bronchospasm and varying time constants from different respiratory units (Figure 8.2C). Another example can be seen in Figure 8.2D in which a "curare cleft" can be seen during phase III indicative of ventilator asynchrony in a patient

attempting to take an inspiratory breath during the expiratory phase of the respiratory cycle.

Pulse oximetry utilizes spectrophotometry to differentiate between oxygenated and deoxygenated hemoglobin and reports a percent saturation (Spo_2) in arterial blood. This is accomplished by utilizing an alternating current amplifier to process pulsatile light transmission using two wavelengths: one in the red region of the light spectrum (~660 nm) and one in the infrared region (~940 nm). Deoxygenated hemoglobin absorbs light in the red region better than oxygenated blood, and the opposite is true in the infrared region. The transmission of these two wavelengths passes through tissue (often the finger or earlobe) and is sensed by a photodetector. The intensity of light transmission reflects the amount of oxygenated and deoxygenated hemoglobin and is reflected in Equation 5:

$$Spo_2 = \frac{Hbo_2}{Hbo_2 + Hb} \times 100 \qquad (5)$$

where Spo_2 is the percent saturation of hemoglobin, Hbo_2 is oxygenated hemoglobin, and Hb is deoxygenated hemoglobin.

Continuous monitoring with pulse oximetry allows for appropriate provision of supplemental oxygen for patients with respiratory failure and can monitor clinical deterioration or recovery. Pulse oximetry measurements may not be accurate in the setting of hypotension, shock, or cold extremities. In addition, pulse oximetry may fail to detect mild hypoxemia in patients with darker skin pigment. In a recent study published in the *New England Journal of Medicine* in 2020, occult hypoxemia, defined as an arterial oxygen saturation of less than 88% despite an Spo_2 of 92% to 96%, was found in 11.7% of Black patients compared to 3.6% of White patients, reflecting current racial bias in pulse oximetry.

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9 Initial Ventilator Setup

Lauren Sattler and Daniel Reynolds

The initiation of mechanical ventilation is a critical period during the course of a patient's stay in the intensive care unit, and initial ventilator settings should be selected to address the most likely underlying pathophysiologic abnormality (Table 9.1). However, the clinician is encouraged to monitor the patient closely during initiation of mechanical ventilation, as this period often provides important answers regarding the underlying cause of the decompensation requiring ventilatory support. The patient's response to mechanical ventilation may also provide further information regarding the severity of the disease process and the likely response to standard therapies. Important metrics to assess include the following:

TABLE 9.1 Guidelines for Initial Ventilator Settings in Different Clinical Scenarios

Indication for Mechanical Ventilation	Mode of Choice	Respiratory Rate (Breaths/min)	Tidal Volume (mL/kg)	Fio_2	PEEP	Additional Ventilator Issues	Adjunctive Therapies	Additional Comments
Airway protection, spontaneously breathing patient (eg, hepatic encephalopathy, upper airway obstruction), postoperative respiratory failure	AC (volume or pressure) SIMV PSV	10-14	6-8	100% initially, obtain ABG and wean for Spo_2 >92% to goal Fio_2 of 40%	5	Peak flow 60 L/min Trigger sensitivity—2 cm H_2O	DVT GI	Maintain on M until upper air issues resolv intra-operativ sedatives/par to clear Patients with hepatic encephalopat are prone to develop respi alkalosis, so T may need to l reduced.
Asthma exacerbation	AC (volume)	Set rate low, 8-12	6-8	100% initially, obtain ABG and wean for Spo_2 >92% to goal Fio_2 of 40%	5	Set peak flows high, allow adequate expiratory time. Consider square wave ventilation. Use flow-by for easier triggering. Allow adequate E time (target I:E ratio of 1:3-1:4).	BD ST AB SDN DVT GI	Tolerate hypercarbia, l peak airway pressures. Monitor for au PEEP and barotrauma. Do not ventila a "normal" AB Apply externa PEEP to over intrinsic PEEP when triggerin Often need h sedation initia Once bronchospasm acute issues adequately resolved, do n prolonged we trials, conside of extubation

Indication for Mechanical Ventilation	Mode of Choice	Respiratory Rate (Breaths/min)	Tidal Volume (mL/kg)	Fio_2	PEEP	Additional Ventilator Issues	Adjunctive Therapies	Additional Comments
COPD exacerbation	AC (volume)	Set rate low, 8-12,	6-8	100% initially, obtain ABG and wean for sats >92% to goal FIO_2 of 40%	5	Set peak flows high, and allow adequate E time (target I:E ratio of 1:3-1:4). Use flow-by for easier triggering	BD ST AB DVT GI NUTR	Monitor for au PEEP. Avoid post-hypercapnic alkalosis. Tolerate hypercarbia; ventilate for a "normal" ABG Monitor for barotrauma. Apply externa PEEP to over intrinsic PEEP when triggerin Consider extubation to NIPPV.
Hypoxemic respiratory failure with pneumonia or pulmonary edema	AC (volume)	Often need high rates, 16-24 because of high V_E requirements	6-8	100% initially, obtain ABG and wean for sats >92% to goal FIO_2 of 40%	5-10	Often have high V_E requirements	BD AB DVT GI NUTR	Secretion management important. In septic patie allow full MVS divert CO from respiratory mu to other vital organs. Follow improvement clinically as improved pulmonary compliance.
ALI/ARDS	AC (volume) PCV, high-frequency oscillator, APRV	Often need high rates, up to 30, because of high V_E requirements	6	100% initially, obtain ABG and wean for sats > 92% to "safe" FIO_2 of <60%	5-15	May need I:E of 1:1 or 1.5:1 (IRV) Need higher mean airway pressures Allow permissive hypercarbia to pH of 7.20.	BD DVT GI NUTR SDN	Consider neb prostacyclin, oxide. Early trial of p ventilation Monitor for barotrauma. Often require heavy sedatio Consider earl neuromuscula blockade for Consider adjunctive ste based on etio Monitor for se complications

Indication for Mechanical Ventilation	Mode of Choice	Respiratory Rate (Breaths/min)	Tidal Volume (mL/kg)	Fio_2	PEEP	Additional Ventilator Issues	Adjunctive Therapies	Additional Comments
Hypoventilation from CNS depression, neuromuscular weakness	AC (volume)	Set rate at 10-16	8-10	100% initially, obtain ABG and wean rapidly for sats of >92% to goal FIO_2 of 30%	5	Peak flow 60 L/min, consider setting low flow trigger in neuromuscular weakness	GI DVT NUTR	Avoid sedativ Prone to atelectasis Follow NIF in patients with weakness.

AB, antibiotics; ABG, arterial blood gas; AC, assist control; APRV, airway pressure release ventilation; BD, bronchodilator; CNS, central nervous system; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis FIO_2, fraction of inspired oxygen; GI, gastrointestinal; I:E, expiratory time ratio; IRV, inverse ratio ventilation; MV, mechanical ventilation; MVS, mechanical ventilator support; NIF, negative inspiratory force; NIPPV, noninvasive positive pressure ventilation; NUTR, nutritional support; OR, operating room; PCV, pressure control ventilation; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; sats, hemoglobin oxygen saturation; SDN, sedation; SIMV, synchronized intermittent mandatory ventilation; ST, steroids; TV, tidal volume; V_E, minute ventilation.

Intubation-related considerations:

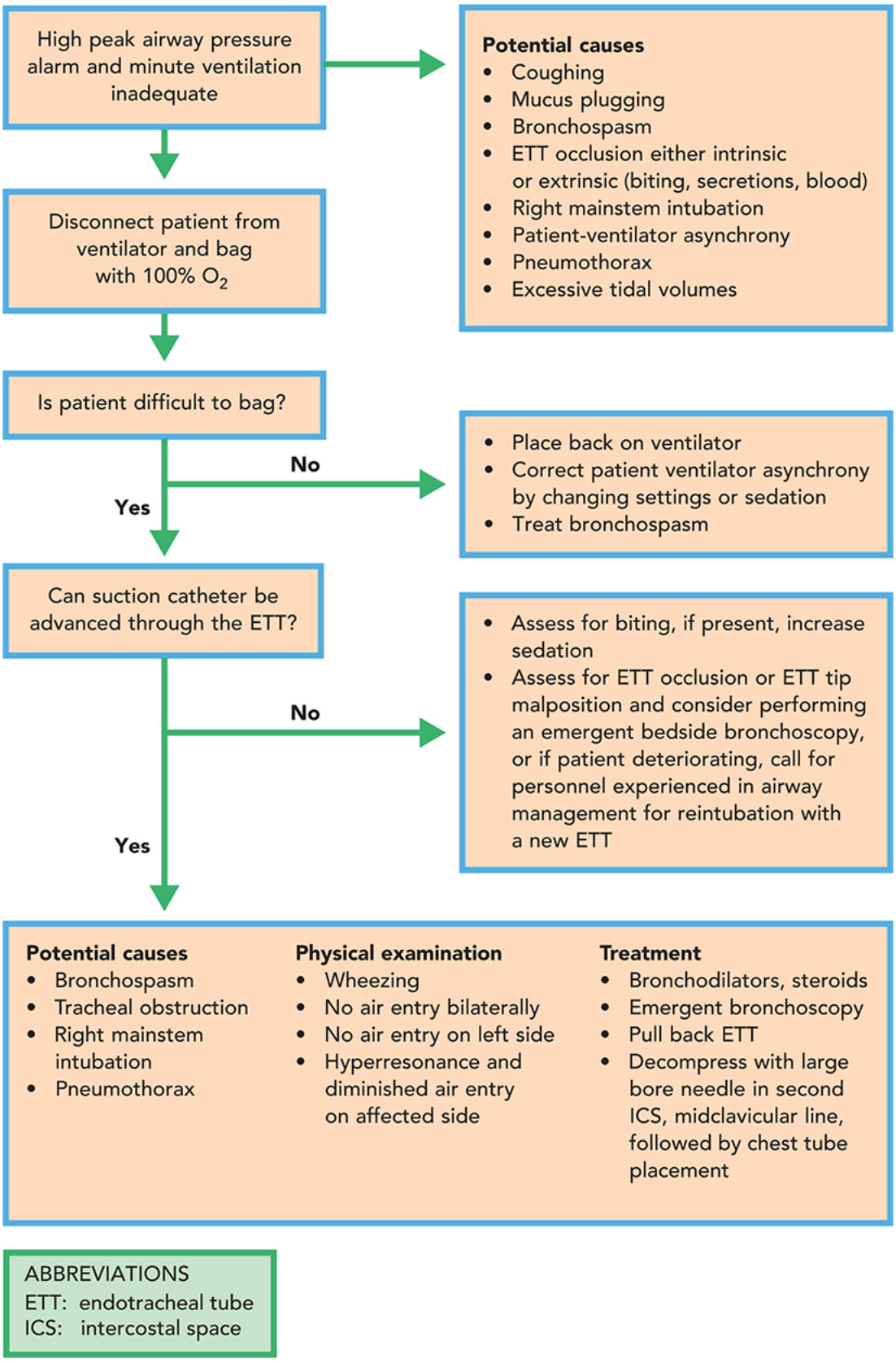
- Endotracheal tube (ETT) positioning: A rough guide is 22 cm at the teeth for a female and 23 cm for a male. This approach, together with careful chest auscultation, can avoid the complications of right mainstem intubation prior to the confirmatory chest x-ray being performed. However, positioning should always be confirmed with a chest x-ray.
- Management after rapid sequence intubation (RSI): If the patient was paralyzed for the intubation with a nondepolarizing neuromuscular blocker, ensure adequate analgesia and sedation during the next hour.

Clinical evaluation postintubation:

- Minute ventilation: Applied minute ventilation should be set to match either the patient's minute ventilation prior to intubation or to a minute ventilation that will appropriately correct the underlying physiologic abnormality. For example, this is very important in patients with septic shock, diabetic ketoacidosis, renal failure, salicylate toxicity, and lactic acidosis, in whom a high minute ventilation will be necessary to avoid acidosis. Conversely, in patients with chronic CO2 retention, if the minute ventilation is set too high, either by an excessive tidal volume or respiratory rate, alkalosis can develop from an excessive acute reduction in $PaCO_2$ (post-hypercapnic alkalosis).
- Airway pressures: Obtaining a sense of the patient's baseline initial airway pressures will help should any respiratory deterioration develop, such as a change in lung compliance, pneumothorax, or mucus plug. An initial plateau pressure (Pplat) obtained after an inspiratory hold should be recorded and, in general, ventilator settings should be adjusted to maintain a Pplat lesser than 30 mm Hg. Additionally, if the peak pressure (Ppeak) is elevated, this should be compared with Pplat to determine further management (Algorithm 9.1). If there is concern for significant obstructive disease, such as asthma or chronic obstructive pulmonary disease (COPD), an expiratory hold maneuver should be performed to assess for intrinsic or auto-positive end-expiratory pressure (iPEEP). Adjustments should be made to the ventilator if significant iPEEP is present in order to avoid further dynamic hyperinflation (Table 9.1).
- Driving pressure: Defined as the ratio of tidal volume to respiratory system compliance, or calculated as the difference between Pplat and PEEP. Recent observational data have identified a potential

survival benefit associated with reduced driving pressure (typically <10-15 mm Hg), for which a titration of PEEP can be performed to determine an optimal PEEP.

ALGORITHM 9.1 **Management Algorithm for High Peak Airway Pressures**


High peak airway pressure alarm and minute ventilation inadequate
Potential causes
• Coughing
• Mucus plugging
• Bronchospasm
• ETT occlusion either intrinsic or extrinsic (biting, secretions, blood)
• Right mainstem intubation
• Patient-ventilator asynchrony
• Pneumothorax
• Excessive tidal volumes
Disconnect patient from ventilator and bag with 100% O_2
Is patient difficult to bag?
No
• Place back on ventilator
• Correct patient ventilator asynchrony by changing settings or sedation
• Treat bronchospasm
Yes
Can suction catheter be advanced through the ETT?
No
• Assess for biting, if present, increase sedation
• Assess for ETT occlusion or ETT tip malposition and consider performing an emergent bedside bronchoscopy, or if patient deteriorating, call for personnel experienced in airway management for reintubation with a new ETT
Yes
Potential causes
• Bronchospasm
• Tracheal obstruction
• Right mainstem intubation
• Pneumothorax
Physical examination
• Wheezing
• No air entry bilaterally
• No air entry on left side
• Hyperresonance and diminished air entry on affected side
Treatment
• Bronchodilators, steroids
• Emergent bronchoscopy
• Pull back ETT
• Decompress with large bore needle in second ICS, midclavicular line, followed by chest tube placement
ABBREVIATIONS
ETT: endotracheal tube
ICS: intercostal space

Capnography:

- Waveform shape: End-tidal co2 ($ETCO_2$) is often measured as a waveform, that is, capnography. Gradual upward sloping ("shark fin" appearance) is consistent with airways obstruction and bronchospasm, whereas sharp upsloping at end exhalation is suggestive of poor compliance.
- $ETCO_2$ value: Elevation in the absolute value of the $ETCO_2$ is usually representative of hypercarbia, while a reduced $ETCO_2$ value is suggestive of respiratory alkalosis that is often secondary to tachypnea from sepsis or compensation for metabolic acidosis. Of note, abnormal $ETCO_2$ measurements should be confirmed with serum blood gas. A large gradient between the $PaCO_2$ obtained from an arterial blood gas and the $ETCO_2$ reflects dead space ventilation, which can be identified in the setting of acute pulmonary embolism.
- Post-cardiac arrest: In a patient post cardiac arrest and resuscitation, a sustained elevation in $ETCO_2$ greater than 15 mm Hg is suggestive of adequate perfusion.

Routine management of the ventilated patient:

- Synchrony: Routine evaluation for ventilator synchrony should be performed with prompt recognition and management of dyssynchrony in order to avoid ventilator-induced lung injury.
- Sedation: A sedation strategy should be chosen based on the patient's underlying physiology and hemodynamics. Anticipated duration of ventilation should also be considered, and daily breathing trials should be performed after pausing sedation once the patient has clinically improved.

Table 9.1 provides a general guideline to the initial ventilator settings in different clinical circumstances. The table is simply a guide, and the reader should understand that every patient is unique and should have the ventilator adjusted according to the individual's clinical status.

Algorithm 9.1 is a management algorithm for troubleshooting persistent high peak airway pressures, a common ventilator-related problem in the intensive care unit. Table 9.2 provides potential causes for an alarm resulting from a low exhaled tidal volume/low minute ventilation.

TABLE 9.2 Potential Causes for a Low Exhaled Tidal Volume/Low Minute Ventilation Alarm

Leak in the circuit
• Tracheal cuff leak • Patient inadvertently extubated or endotracheal tube tip high • Ventilator circuit disconnected at any point from the patient to the ventilator • Large bronchopleural fistula with a leak through a chest tube
In patients on pressure support ventilation
• Worsening respiratory system compliance • Decreased patient effort • Decreased patient respiratory rate • Inadequate pressure support being provided • In patients on pressure control ventilation • Worsening respiratory system compliance

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10 Upper Airway Obstruction

Tej M. Patel and Marin H. Kollef

Acute upper airway obstruction is a medical emergency that requires rapid evaluation of the patient with simultaneous therapy to ensure adequate oxygenation and ventilation of the patient. Prompt recognition of premonitory symptoms and signs may enable the physician to buy precious time for evaluation and planning patient care. Common symptoms include cough, hoarseness, dyspnea, stridor, nasal flaring, use of accessory muscles, intercostal retractions with progression to cyanosis, and unresponsiveness. Stridor in particular is a serious sign, signifying at least 25% narrowing of the airway and likely at least 50% narrowing if the patient is in distress. The common causes of upper airway obstruction are presented in Table 10.1, and the steps for the rapid assessment and management of the patient are presented in Algorithm 10.1. It is important to note that with most patients, upper airway obstruction is a clinical diagnosis that does not allow significant time for laboratory testing, arterial blood gas analysis, or even imaging in the acute setting, and all resources should be directed to preventing cardiorespiratory arrest and securing the airway. Figures 10.1 to 10.3 review the anatomic landmarks of the upper airway, a basic cricothyroidotomy set, and illustrate practical aspects of performing emergent surgical airway access.

TABLE 10.1 Etiology and Specific Therapy of Upper Airway Obstruction by Site

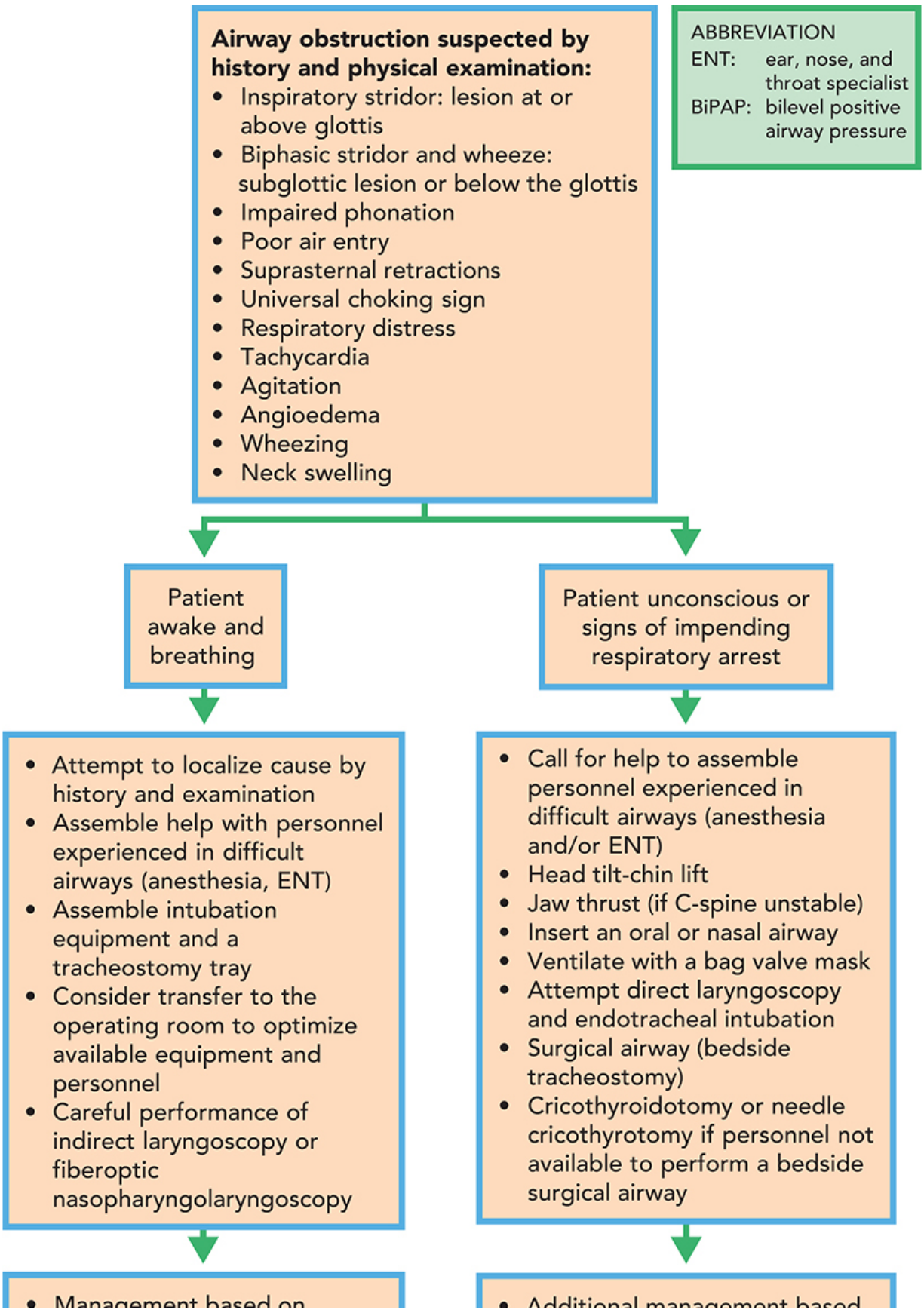
Site of Obstruction	Etiology	Specific Therapy

Site of Obstruction	Etiology	Specific Therapy
Nasopharynx	Nasal polyps	Nasal steroids, surgery
	Nasal tumors, lymphoma	Radiation, surgery, chemotherapy
	Adenoidal hypertrophy	Adenoidectomy
	Trauma	Fracture reduction, incise hematomas
	Nasal packing	Prophylactic antibiotics for sinusitis, humidified oxygen
Oropharynx	Ludwig angina	Antibiotics, drainage, may need tracheotomy
	Odontogenic abscess	Antibiotics and drainage
	Retropharyngeal abscess	Antibiotics and drainage
	Peritonsillar abscess	Tonsillectomy
	Tonsillar enlargement	Supportive, tracheotomy
	Macroglossia	Antihistamines, steroids, epinephrine (see “Angioedema” section)
	Angioedema	
	Stevens-Johnson syndrome	Supportive care, tracheotomy
	Burkitt lymphoma	Chemoradiation
	Salivary tumors	Resection
	Le Fort fractures 2 and 3	Tracheotomy, fixation
	Obstructive sleep apnea	CPAP, UPPP, tracheotomy

Site of Obstruction	Etiology	Specific Therapy
Laryngopharynx	Epiglottitis	Antibiotics
	Acute bacterial laryngotracheitis (diphtheria)	Antibiotics
	Neoplasms: SCC, papillomatosis	Resection, laser removal
	Angioedema	Antihistamines, steroids, epinephrine (see “Angioedema” section)
	Rheumatoid arthritis	Corticosteroids, tracheotomy
	Relapsing polychondritis	Corticosteroids, tracheotomy
	Wegener granulomatosis	Corticosteroids, cyclophosphamide, tracheotomy
	Midline granuloma	Radiation
	ETT injury: subglottic stenosis	Resection, dilation, cryotherapy
	Trauma, burns, inhalation injury	Tracheotomy
	Hemangiomas	Laser, intralesional steroids, tracheotomy
	Foreign body aspiration, dislodged tooth	Endoscopy
	Iatrogenic: laryngospasm, epistaxis	Supportive

CPAP, continuous positive airway pressure; ETT, endotracheal tube; SCC, squamous cell carcinoma; UPPP, uvulopalatopharyngoplasty.

ALGORITHM 10.1 Management of a Patient With Airway Obstruction


Airway obstruction suspected by history and physical examination:
• Inspiratory stridor: lesion at or above glottis
• Biphasic stridor and wheeze: subglottic lesion or below the glottis
• Impaired phonation
• Poor air entry
• Suprasternal retractions
• Universal choking sign
• Respiratory distress
• Tachycardia
• Agitation
• Angioedema
• Wheezing
• Neck swelling
ABBREVIATION
ENT: ear, nose, and throat specialist
BiPAP: bilevel positive airway pressure
Patient awake and breathing
Patient unconscious or signs of impending respiratory arrest
• Attempt to localize cause by history and examination
• Assemble help with personnel experienced in difficult airways (anesthesia, ENT)
• Assemble intubation equipment and a tracheostomy tray
• Consider transfer to the operating room to optimize available equipment and personnel
• Careful performance of indirect laryngoscopy or fiberoptic nasopharyngolaryngoscopy
• Call for help to assemble personnel experienced in difficult airways (anesthesia and/or ENT)
• Head tilt-chin lift
• Jaw thrust (if C-spine unstable)
• Insert an oral or nasal airway
• Ventilate with a bag valve mask
• Attempt direct laryngoscopy and endotracheal intubation
• Surgical airway (bedside tracheostomy)
• Cricothyroidotomy or needle cricothyrotomy if personnel not available to perform a bedside surgical airway
• Management based on
• Additional management based

diagnosis
- Can use heliox or BiPAP if etiology not progressive
- Close monitoring

on etiology

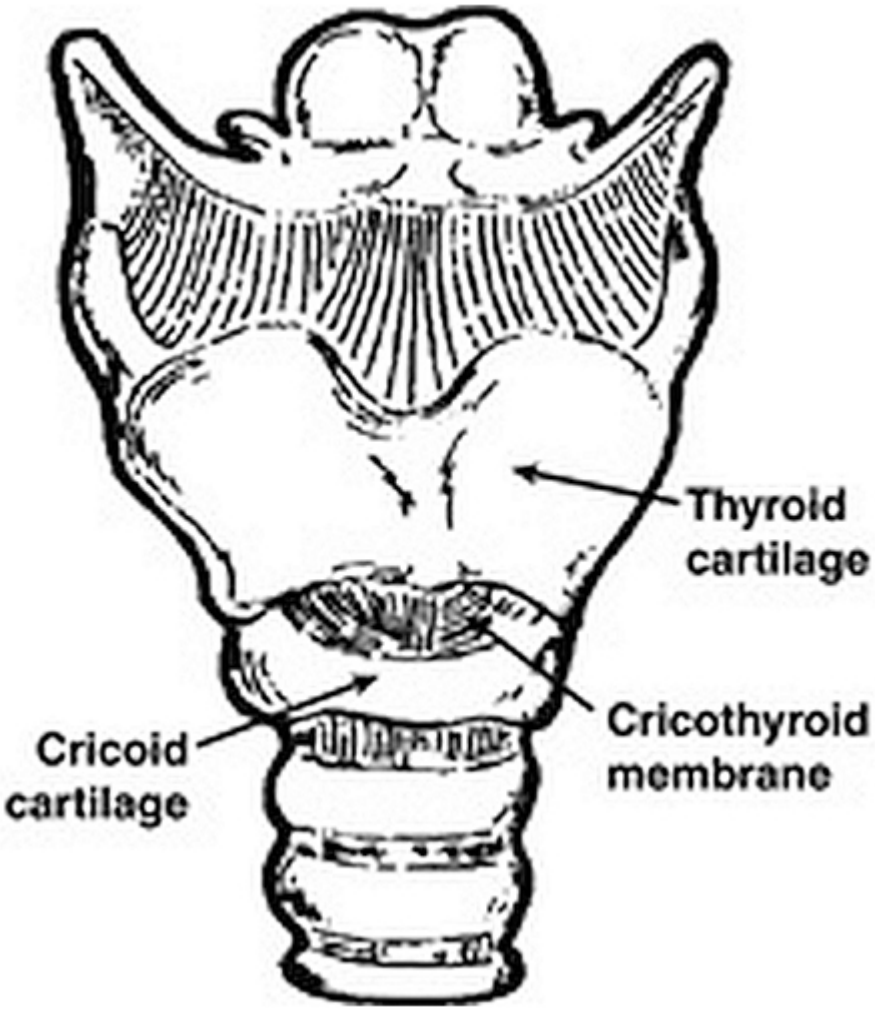


FIGURE 10.1 **Anatomic landmarks used for a cricothyroidotomy.**

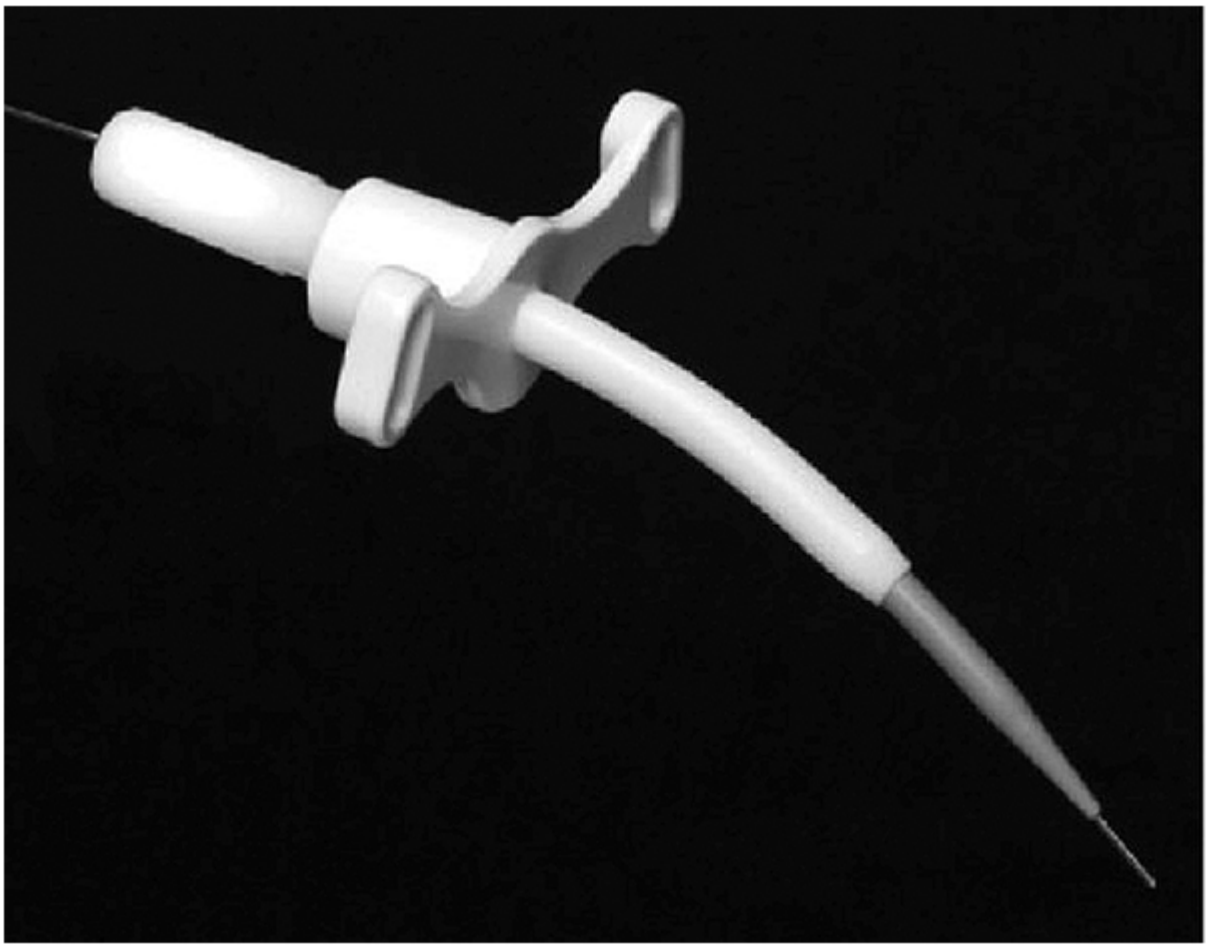


FIGURE 10.2 **A typical Seldinger technique commercially available cricothyroidotomy set with guidewire, dilator, and cricothyroidotomy device.** (Used with permission from Singh-Radcliff N. *5-Minute Anesthesia Consult*. Wolters Kluwer/Lippincott Williams & Wilkins; 2012.)

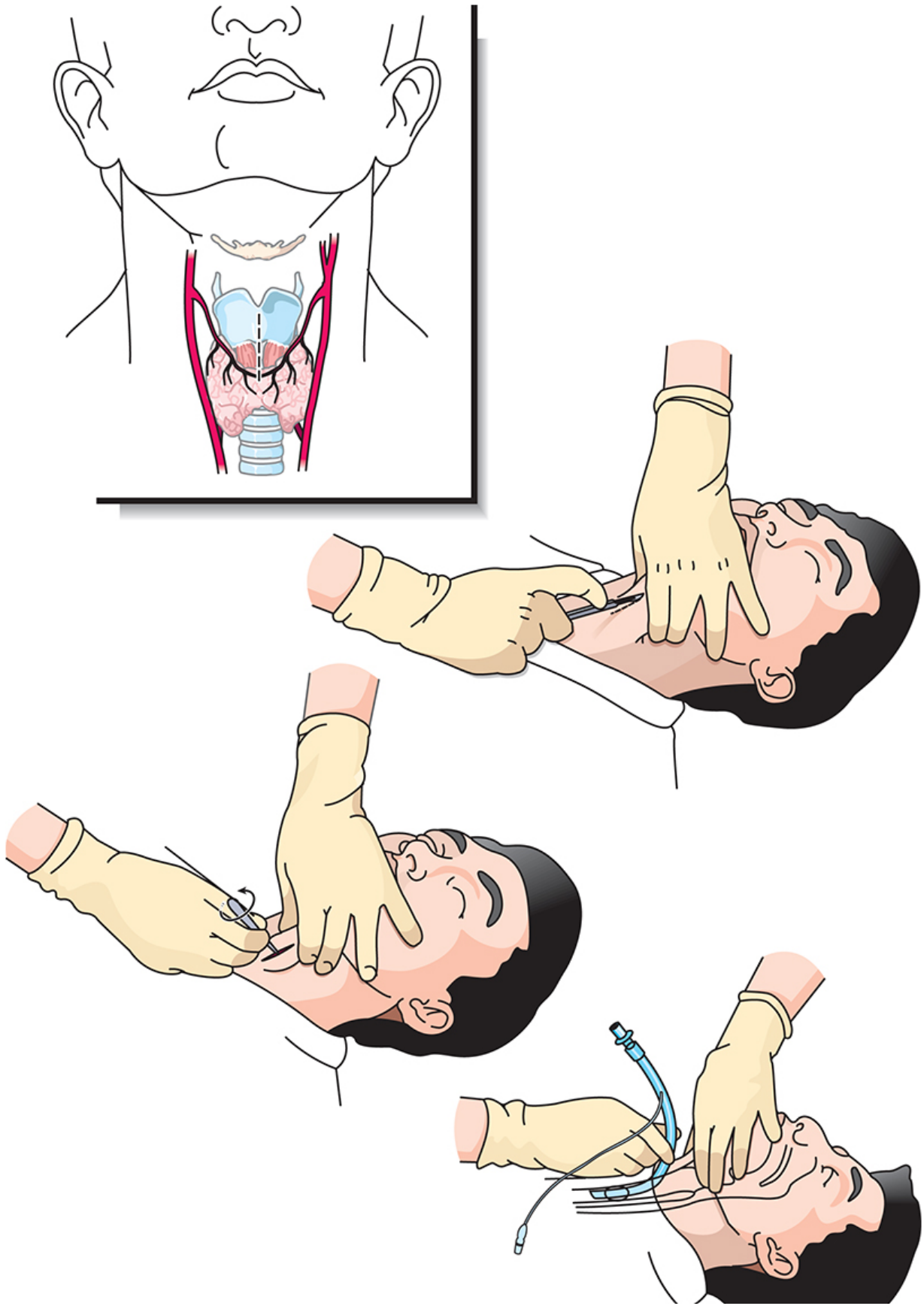


FIGURE 10.3 **Basic steps in performing a cricothyroidotomy.** (From LifeART image copyright © 2016. Lippincott Williams & Wilkins. All rights reserved.)

Some common etiologies and their management will be briefly reviewed.

Infectious Epiglottitis and Laryngitis

Routine pediatric vaccination against *Haemophilus influenzae* has now made epiglottitis more common in adults than in children. The potential pathogens that cause epiglottitis include *H. influenzae* and *Haemophilus parainfluenzae*, *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus*, and occasionally anaerobic organisms. Laryngitis is often caused by viruses and rarely *Corynebacterium diphtheriae*, which is more common in unvaccinated individuals.

The classic presentation is of an adult who is drooling, appears toxic, and is sitting upright in the tripod position. In cases of epiglottitis, the epiglottis appears swollen and beefy. Diphtheria is characterized by a gray pseudomembrane covering the posterior pharynx. Blood cultures may occasionally be positive for bacteria, and a lateral radiograph of the neck may show the swollen epiglottis (termed “thumbprint sign”) and narrowed vallecula. These patients have a high potential for complete occlusion of the airway and should be treated with empiric intravenous (IV) antibiotics, such as ceftriaxone 2 grams every 24 hours or ampicillin-sulbactam 1.5 to 3 grams every 6 hours. There is no evidence to support the use systemic steroids in these patients, but in certain clinical scenarios, it may be reasonable to administer methylprednisolone or dexamethasone at low to intermediate doses.

Most patients improve rapidly with antibiotics and failure to improve should raise concern for the development of a soft tissue

abscess in the parapharyngeal space. Patients with diphtheria should also receive equine antitoxin and a macrolide antibiotic. Personnel with experience in handling difficult airways should be called in to evaluate the patient, and an emergency tracheostomy set should be brought into the examining room. If an examination is to be performed fiberoptically, preferentially this should be done with a backup plan and equipment in place, should the patient require conversion to a surgical airway. The examination needs to be performed cautiously so as not to precipitate further narrowing of the airway.

Angioedema

Angioedema can occur through a variety of mechanisms and results in painless swelling of the soft tissues of the face. The common precipitants are angiotensin-converting enzyme inhibitors, immunoglobulin E–mediated allergic reactions to foods or medications, and complement activation through an inherited or acquired C1 esterase inhibitor deficiency/impairment.

The mainstays of treatment include stopping the offending medication, antihistamines, steroids, and epinephrine, with airway management as noted in the algorithm. Of note, these pharmacologic interventions do not impact the bradykinin pathway, and are therefore of questionable efficacy, but are routinely administered due to occasional diagnostic uncertainty, and clinical concern for anaphylaxis. Patients with hereditary deficiency of C1 esterase inhibitor respond to early therapy with icatibant (a selective bradykinin B2 receptor antagonist). Additional options for these patients include fresh frozen plasma (which contains small amounts of C1 esterase inhibitor), purified C1 inhibitor concentrate, or ecallantide (a kallikrein inhibitor).

Postextubation Stridor

Stridor occurs in up to 15% of patients after extubation, and most cases are caused by laryngeal edema. Laryngospasm and secretions in the airway are less common causes of stridor in this situation.

Risk factors for the development of postextubation laryngeal edema include traumatic intubations, female gender, prolonged intubation, use of larger bore endotracheal tubes, history of difficult intubation, and high endotracheal tube cuff pressures.

Prevention of postextubation laryngeal edema includes measures to choose the appropriate size endotracheal tube for the patient's airway and monitoring of endotracheal tube cuff pressures to keep the cuff pressure below 25 mm Hg. In addition, attention should be paid to the patient's chest radiograph to ensure that the cuff is not positioned in the subglottic space, but rather in the more distal trachea.

Pre-extubation assessment of airway patency can be performed by utilizing a cuff leak test, a simple, noninvasive bedside test, utilizing the difference in inhaled tidal volumes and exhaled tidal volumes, with the cuff deflated. The patient's upper airway should be thoroughly suctioned prior to the test and the trachea suctioned after cuff deflation to avoid aspiration of secretions from the oropharynx and accumulated secretions above the endotracheal tube cuff. The sensitivity and specificity of this test vary greatly in clinical trials and depend on the leak cutoff value chosen. Overall, the cuff leak test is useful in identifying patients at low risk for postextubation laryngeal edema (high negative predictive value). Additional methods of airway evaluation include the use of ultrasound to assess air column width and video laryngoscopy or flexible endoscopy; however, these techniques have not been validated in large patient populations.

In patients who do not have a leak and have additional risk factors for postextubation laryngeal edema as noted earlier, at least two doses of prophylactic steroids, with the first dose given from 4 hours to preferably at least 12 hours pre-extubation, are recommended. This strategy has reduced the risk of postextubation laryngeal edema.

In a patient where there is significant concern for airway patency after extubation, an airway exchange catheter can be left in place after extubation. These catheters provide for the ability to replace the endotracheal tube over the catheter in case intubation is difficult and some devices allow for the provision of supplemental oxygen and limited ventilation. Experience in the use of these devices is important with particular attention paid to depth of insertion to avoid pneumothoraces.

Immediate management of the patient who develops acute postextubation laryngeal edema should consist of nebulized racemic epinephrine, which will cause local vasoconstriction and reduce edema. Most physicians also use short courses (48 hours) of IV corticosteroids; however, there are no randomized data to support this treatment. In patients who exhibit signs of respiratory distress, the safest option is reintubation to secure the airway. Additional options to consider in patients who are not in distress include heliox, which lowers airway resistance and may reduce work of breathing, allowing time for steroids to work. The use of noninvasive ventilation in carefully selected patients has been described, however, in patients who exhibit signs of distress and who have progressive airway narrowing, delaying intubation can be hazardous and these strategies should be used with caution.

SUGGESTED READINGS

Bas M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med.* 2015;372:418-425.

Subcutaneous icatibant resulted in faster resolution of angioedema compared to patients who only received steroids and antihistamines.

Eskander A, de Almeida JR, Irish JC. Acute upper airway obstruction. *N Engl J Med.* 2019;20:1940-1949

An excellent review on upper airway obstruction.

Heidegger, T. Management of the difficult airway. *N Engl J Med*. 2021;19:1836-1847.

An excellent review that defines a difficult airway, predictors of a difficult airway, as well as, management of issues related to difficult airways.

11 The Acute Respiratory Distress Syndrome

John C. Grotberg and Bryan D. Kraft

The acute respiratory distress syndrome (ARDS) is a life-threatening cause of respiratory failure. It is characterized by the acute onset of protein-rich pulmonary edema, bilateral alveolar opacities, and hypoxemia. The incidence of non–COVID-19 ARDS in the United States is estimated to be 200,000 cases per year, with a mortality rate ranging from 35% to 40%. This rate marks a significant decrease from the 65% to 70% mortality rate observed in the early 1980s. Cases of ARDS significantly increased following the COVID-19 pandemic, with pneumonia affecting up to 15% to 20% of patients and ARDS occurring in as many as 5% of patients. While the major physiologic consequence of ARDS is hypoxemia due to a high shunt fraction and ventilation-perfusion mismatches, most patients ultimately die from the underlying cause (eg, sepsis) or associated complications (eg, multiorgan failure) rather than from refractory hypoxemia per se. The current therapies for ARDS centers around treatment of the underlying cause, using a pressure-targeted strategy of low tidal volume ventilation to prevent further lung injury, employing prone positioning, and implementing appropriate fluid management.

In 1994, the American-European Consensus Conference (AECC) on ARDS convened to develop a set of diagnostic criteria for ARDS. In 2012, a modified definition of ARDS called the Berlin Definition was developed and validated, as shown in Table 11.1. With these criteria, in conjunction with the more recent view that there is little importance in the distinction between acute lung injury (ALI) and ARDS, along with evolving changes in the use of hemodynamic monitoring (see later discussion), the diagnosis of ARDS should be

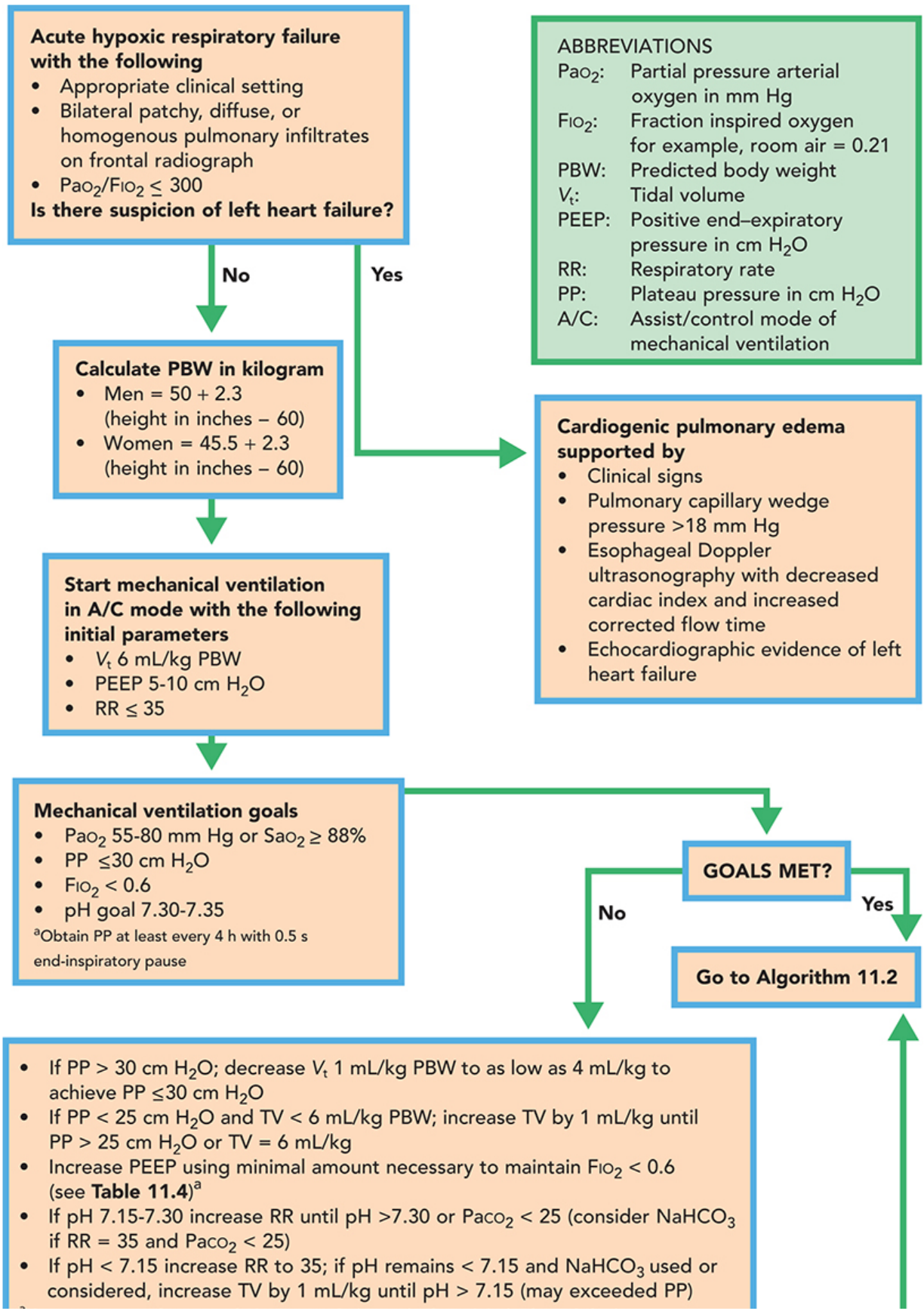
considered whenever the following criteria are met (Algorithm 11.1): (a) an appropriate clinical setting (ie, a likely underlying cause); (b) the development of bilateral alveolar and/or interstitial infiltrates of acute onset (<1 week) on frontal chest radiograph or computed tomography (CT) scan; (c) a ratio of the partial pressure of arterial oxygen pressure in millimeters of mercury (Pa_{O_2}) divided by the fraction of inspired oxygen (F_{IO_2}) of 300 or less; and (d) no clinical evidence that left ventricular failure or intravascular volume overload is the principle cause for acute radiographic pulmonary infiltrates.

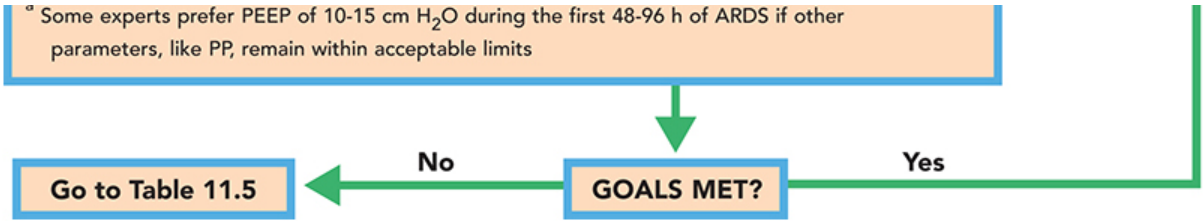
TABLE 11.1 The Berlin Definition of ARDS

Timing/onset	Within 1 wk of a known clinical insult (see Table 11.2) or new or worsening respiratory symptoms
Chest radiograph/computed tomography	Bilateral opacities not fully explained by effusions, lobar collapse, or nodules
Origin of edema/opacities	Cannot fully be explained by cardiac pump failure or fluid overload. Needs objective measure (eg, echocardiography, transthoracic/esophageal Doppler, pulmonary artery catheter) to exclude hydrostatic edema if no risk factors for ARDS present
Impaired oxygenation	Mild: 200 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O Moderate: 100 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O Severe: Pa_{O_2}/F_{IO_2} ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of arterial oxygen; PEEP, positive end–expiratory pressure.

ALGORITHM 11.1 Ventilator Management in Acute Lung Injury/Acute Respiratory Distress Syndrome


Acute hypoxic respiratory failure with the following
• Appropriate clinical setting
• Bilateral patchy, diffuse, or homogenous pulmonary infiltrates on frontal radiograph
• $Pao_2/Fio_2 \leq 300$
Is there suspicion of left heart failure?
No
Yes
ABBREVIATIONS
Pao_2: Partial pressure arterial oxygen in mm Hg
Fio_2: Fraction inspired oxygen for example, room air = 0.21
PBW: Predicted body weight
V_t: Tidal volume
PEEP: Positive end–expiratory pressure in cm H_2O
RR: Respiratory rate
PP: Plateau pressure in cm H_2O
A/C: Assist/control mode of mechanical ventilation
Calculate PBW in kilogram
• Men = 50 + 2.3 (height in inches – 60)
• Women = 45.5 + 2.3 (height in inches – 60)
Cardiogenic pulmonary edema supported by
• Clinical signs
• Pulmonary capillary wedge pressure >18 mm Hg
• Esophageal Doppler ultrasonography with decreased cardiac index and increased corrected flow time
• Echocardiographic evidence of left heart failure
Start mechanical ventilation in A/C mode with the following initial parameters
• V_t 6 mL/kg PBW
• PEEP 5-10 cm H_2O
• RR ≤ 35
Mechanical ventilation goals
• Pao_2 55-80 mm Hg or $Sao_2 \geq 88\%$
• PP ≤30 cm H_2O
• $Fio_2 < 0.6$
• pH goal 7.30-7.35
[a]Obtain PP at least every 4 h with 0.5 s end-inspiratory pause
GOALS MET?
No
Yes
Go to Algorithm 11.2
• If PP > 30 cm H_2O; decrease V_t 1 mL/kg PBW to as low as 4 mL/kg to achieve PP ≤30 cm H_2O
• If PP < 25 cm H_2O and TV < 6 mL/kg PBW; increase TV by 1 mL/kg until PP > 25 cm H_2O or TV = 6 mL/kg
• Increase PEEP using minimal amount necessary to maintain $Fio_2 < 0.6$ (see Table 11.4)[a]
• If pH 7.15-7.30 increase RR until pH >7.30 or $Paco_2 < 25$ (consider $NaHCO_3$ if RR = 35 and $Paco_2 < 25$)
• If pH < 7.15 increase RR to 35; if pH remains < 7.15 and $NaHCO_3$ used or considered, increase TV by 1 mL/kg until pH > 7.15 (may exceeded PP)


[a] Some experts prefer PEEP of 10-15 cm H_2O during the first 48-96 h of ARDS if other parameters, like PP, remain within acceptable limits
GOALS MET?
No
Yes
Go to Table 11.5

ARDS can arise from direct injury to the lung parenchyma or from indirect systemic insults transmitted to the lung by the pulmonary circulation (Table 11.2). Direct causes of ARDS include pneumonia, gastric aspiration, blunt chest trauma, near drowning, and toxic inhalations. Common indirect causes include sepsis, large-volume blood transfusions (typically >15 Units), massive tissue trauma, lung transplantation, ischemia-reperfusion after cardiopulmonary bypass or lung transplantation, drug overdoses, and pancreatitis. Although more than 60 conditions have been associated with ARDS, the most frequent cause is sepsis, followed by pneumonia and aspiration.

TABLE 11.2 Common Causes of ARDS

Direct Causes	Indirect Causes
Pneumonia	Sepsis
Aspiration	Severe traumatic shock
Inhalation injuries	Large-volume blood transfusions (>15 Units) (TRALI)
Blunt pulmonary trauma	Pancreatitis
Near drowning	Ischemic-reperfusion injury after cardiopulmonary bypass or lung transplantation
Drug toxicities/overdoses; narcotics, tricyclic antidepressants, chemotherapeutic agents, fat emulsion, amiodarone	

ARDS, acute respiratory distress syndrome; TRALI, transfusion-related acute lung injury.

The pathogenesis of ARDS starts with a pulmonary or systemic insult that triggers an inflammatory response within the lungs. The resulting “noncardiogenic, increased permeability” form of pulmonary edema arises due to break down of the alveolar-capillary barrier and

follows a predictable clinical and pathologic course that has been separated into three clinically meaningful phases. The exudative phase occurs immediately and lasts approximately 3 to 7 days. Pathologically, the classic pattern observed is “diffuse alveolar damage,” seen in about half of cases, and is characterized by (a) infiltration of inflammatory cells (neutrophils) into the interstitial and alveolar spaces, (b) accumulation of extravascular lung water and plasma proteins (fibrin) that precipitate into the characteristic intra-alveolar “hyaline membranes,” (c) type 1 alveolar epithelial cell necrosis, and (d) intra-alveolar hemorrhage. Some believe that the formation of hyaline membranes is caused principally by oxygen toxicity. The physiologic consequences of filling alveoli with edema and cellular debris are reduced alveolar ventilation, intrapulmonary shunting, and reduced lung compliance with increased work of breathing. The clinical consequences are a need for mechanical ventilatory support to reduce the work of breathing, a high F_{IO_2} to achieve an acceptable Pa_{O_2}, and positive airway pressure throughout the respiratory cycle (ie, positive end–expiratory pressure or PEEP) to improve alveolar ventilation and reduce atelectasis.

Overlapping with the late exudative phase is a proliferative phase, which usually lasts another 2 to 3 weeks. This phase is characterized by an increase in type 2 pneumocytes, clearance of alveolar edema and debris by macrophage phagocytosis, leading to improved gas exchange, and, eventually, liberation from mechanical ventilation.

Finally, some patients may progress after 2 to 3 weeks to a clinically obvious fibrotic phase. In this phase, patients develop progressive interstitial and alveolar fibrosis, occasionally accompanied by large emphysematous bullae that are prone to rupture. This leads to prolonged ventilator dependency with increased morbidity and mortality. However, progression to fibrosis has decreased with the use of lung-protective modes of ventilation.

ARDS must be distinguished from cardiogenic pulmonary edema and other less common causes of diffuse pulmonary infiltrates due to differences in treatment. If the underlying cause of the acute

pulmonary infiltrates is not certain, then CT, bronchoalveolar lavage, or other diagnostic tests should be performed to exclude entities such as diffuse alveolar hemorrhage, acute interstitial pneumonia, disseminated cancer, acute eosinophilic pneumonia, miliary tuberculosis, and cryptogenic organizing pneumonia (Table 11.3). Although radiographically and physiologically similar, diffuse alveolar damage is not a prominent pathologic feature of these other disease entities.

TABLE 11.3 Conditions Mimicking Acute Respiratory Distress Syndrome

Cardiogenic pulmonary edema	Acute eosinophilic pneumonia
Diffuse alveolar hemorrhage	Miliary tuberculosis
Acute interstitial pneumonia	Cryptogenic organizing pneumonia
Acute pulmonary alveolar proteinosis	Disseminated cancer

ARDS is a widely heterogeneous syndrome, and recent evidence suggests that patients may be subdivided into distinct phenotypes. A retrospective analysis of the ARMA and ALVEOLI trials using latent class analysis identified two phenotypes: (1) hyperinflammatory, characterized by a higher presence of inflammatory plasma biomarkers, vasopressor use, and sepsis, and (2) hypoinflammatory, where these features are less conspicuous or absent. The hyperinflammatory phenotype had higher mortality (44% compared to 23%) and fewer ventilator-free days. Further analysis showed a differential response between phenotypes when comparing high versus low PEEP strategies. High PEEP improved mortality in the hyperinflammatory group, whereas it worsened mortality in the hypoinflammatory group. Further research in subphenotyping ARDS may ultimately lead to targeted interventions based on specific patient characteristics and phenotypes.

The evidence base for a particular strategy of mechanical ventilatory support for ARDS was greatly strengthened in 2000 by the landmark ARMA clinical trial conducted by the National Institutes

of Health ARDS Network. This trial demonstrated a 22% relative reduction in mortality when tidal volumes of 6 mL/kg of predicted body weight (PBW) were used rather than more traditional volumes of 12 mL/kg. The lower tidal volumes are thought to prevent microscopic barotrauma to relatively normal alveoli, which can worsen the extent and/or severity of inflammatory pulmonary edema, an outcome known as *ventilator-induced lung injury.*

The other major aspect of mechanical ventilatory support concerns the use of PEEP. PEEP increases the amount of aerated lung by tidal recruitment, thereby improving oxygenation by decreasing the shunt fraction, allowing a lower F_{IO_2} to be used. However, it can also be associated with barotrauma, overdistension, reduced venous return, and depressed right ventricular function. Because of these potentially conflicting effects, another major clinical trial (ALVEOLI) was conducted by the ARDS Network to determine the relative benefit of high versus low PEEP. The results of this study showed no difference in outcomes between higher PEEP (mean, 13.2 cm H_2O) and lower PEEP (mean, 8.3 cm H_2O) levels. Thus, some recommend that the lowest level of PEEP be used to support oxygenation and to maintain an F_{IO_2} at or below 0.6. However, a meta-analysis of three trials examining lower versus higher levels of PEEP found a survival advantage in the subset of patients with ARDS ($Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg) who received higher levels of PEEP. Therefore, some experts favor higher (10-15 cm H_2O) rather than lower (5-10 cm H_2O) PEEP during the early phase of ARDS (Table 11.4). More recently, an analysis of 3,562 patients with ARDS demonstrated that driving pressure (plateau pressure—PEEP), a measure where tidal volume is normalized to functioning lung size, best stratified risk in ARDS. Adjusting the ventilator (lowering tidal volume, raising PEEP) to reduce driving pressure (targeting below 15-17 cm H_2O) was strongly associated with survival. Some experts advocate for an individualized approach to PEEP that produces the best lung-ventilator mechanics for the patient. This can be accomplished by monitoring driving pressure with PEEP titration,

using the stress index (by analyzing the pressure-time curve waveform), or using electrical impedance tomography (EIT).

TABLE 11.4 Suggested Combinations of F_{IO_2} and PEEP in ARDS

F_{IO_2}	0.3	0.4	0.5	0.6
PEEP	5	5-8	8-10	10
F_{IO_2}	0.7	0.8	0.9	1.0
PEEP	10-14	14	14-18	18-23

ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; PEEP, positive end–expiratory pressure.

Other ventilation strategies can be used as "rescue" therapies when oxygenation is inadequate, despite the previously mentioned approach to ventilatory support, or when patients require unacceptable levels of F_{IO_2} or airway pressure. These include prone ventilation, inverse ratio ventilation, airway pressure release ventilation, neuromuscular blockade (NMB), high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), or inhalational prostacyclin or nitric oxide (Table 11.5). Among these, only prone ventilation, NMB, and ECMO have been associated with mortality improvement in specific patient populations, while HFOV, as demonstrated in the OSCILLATE trial, has been associated with harm.

TABLE 11.5 Treatment for Refractory Hypoxemia in ARDS

Rescue therapies indicated when Pao_2 < 55 mm Hg or Sao_2 < 88% with

- F_{IO_2} > 0.7 or
- PP > 30 cm H_2O

Prone ventilation[a]

- Contraindications:
- Open wounds/burns on the ventral body surface
- Unstable fractures
- Spinal instability
- Increased intracranial pressure
- Hemodynamic instability
- Caution if tracheostomy, chest tubes, obesity, ascites
- Maintain in prone position for 16-20 h of every 24

Other adjunctive/salvage ventilator strategies

- Neuromuscular blockade
- Inverse ratio ventilation (inspiratory time > expiratory time)
- Airway pressure release ventilation
- High-frequency ventilation (may increase mortality)

Extracorporeal membrane oxygenation[a,b]

- Indications (based on EOLIA inclusion criteria)
  - P/F < 50 mm Hg for more than 3 h *or* P/F < 80 mm Hg for more than 6 h despite optimization of mechanical ventilation and adjunctive measures (F_{IO_2} ≥ 80%, PEEP ≥ 10, V_t ≤ 6 mL/kg) *or*
- pH < 7.25 *and* P_{CO_2} > 60 while maintaining plateau pressure < 32 with a maximum RR of 35 breaths per minute
- Absolute contraindications
- Anticipated nonrecovery without a viable plan for decannulation
- Relative contraindications
- Central nervous system hemorrhage or severe central nervous system injury
- Systemic bleeding
- Contraindications to anticoagulation
- Immunosuppression
- Age > 70 y
- Prolonged mechanical ventilation (>7 d with PP > 30 cm H_2O *and* F_{IO_2} > 90%)

Steroids

- 1-7 d of onset of ARDS, but ideally ≤72 h
- No definitive role yet identified unless documented adrenal insufficiency
- Give methylprednisolone (or equivalent) 1 mg/kg IV bolus, then 1 mg/kg/d continuous IV infusion for 14 d *or* give 20 mg IV dexamethasone daily for 5 d followed by 10 mg IV dexamethasone daily for 5 d
- If receiving paralytics, consider delaying use until concomitant use of paralytic agents is not required
- If no clear physiologic or radiologic benefit in 3-5 d, discontinue
- If giving methylprednisolone, after 14 d or successful patient extubation, decrease to 0.5 mg/kg/d IV and continue for 7 d, then decrease to 0.25 mg/kg/d IV and continue for 7 d, then stop
- 7-14 d of onset of ARDS, if steroids were not started earlier
- Benefit less certain, but in select cases may try the same protocol as above. If no clear physiologic or radiologic benefit in 3-5 d, discontinue
- 14 d of onset of ARDS
- Probably no role for steroid use in these cases (may cause increased mortality if used routinely in this time course). However, a trial may still be considered in select cases.

Inhaled pharmacologic agents[c]

- Inhaled epoprostenol
- Inhaled nitric oxide
- Inhaled iloprost (prostaglandin I_2)

ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction inspired oxygen; IV, intravenously; Pa_{O_2}, arterial oxygen pressure in millimeters of mercury; P_{CO_2}, partial pressure of carbon dioxide; PEEP, positive end–expiratory pressure; PP, plateau pressure in centimeters of H_2O; RR, respiratory rate; Sa_{O_2}, oxygen saturation in percent; V_t, tidal volume.

[a]Recent trials suggest survival advantage.

[b]Should be considered in case of severe single-organ dysfunction.

[c]These agents should not be given IV as they may worsen shunting by vasodilating capillaries in nonaerated alveoli.

The prone position improves oxygenation and ventilatory mechanics by improving lung heterogeneity, allowing for increased lung recruitment, ventilation-perfusion matching, and decreased overdistension and lung stress. The PROSEVA trial, which included moderate-to-severe ARDS cases with Pa_{O_2}/F_{IO_2} (P/F) < 150 mm Hg and F_{IO_2} ≥ 0.6, demonstrated a 28-day mortality of 16% in the proning group compared to 32.8% in the supine group. Additionally, the 90-day mortality in the proning group was 23.6% compared to 41% in the supine group. Contraindications to proning include acute bleeding, facial trauma, spinal instability, increased intracranial pressure, recent tracheostomy, or sternotomy within the past 2 weeks.

NMB improves oxygenation by decreasing oxygen consumption, thereby increasing mixed venous oxygen saturation (Sv_{O_2}), eliminating ventilator dyssynchrony, and improving thoracopulmonary compliance. The ACURASYS trial in 2010 demonstrated a mortality benefit with 48 hours of NMB with cisatracurium in patients with moderate-to-severe ARDS (P/F < 150 mm Hg); however, a larger multicenter trial in 2019, the ROSE trial, reported no significant mortality benefit from using NMB in patients with moderate-to-severe ARDS. While it is evident that NMB improves oxygenation, whether it confers mortality benefit is controversial. The ROSE trial excluded patients for whom clinicians already felt there was a clinical indication for NMBs, suggesting that an indiscriminant use of NMB might be less beneficial than a patient-targeted approach.

Veno-venous ECMO (further reading in Chapter 89, ECLS) provides extracorporeal gas exchange in patients with refractory respiratory failure. Two large prospective randomized trials for ECMO in patients with ARDS include the CESAR trial and EOLIA trial. In the CESAR trial, patients were randomized to usual care or transferred to an ECMO center. Of the patients transferred to an ECMO center, 25% responded to optimization of conventional ventilation alone and did not require ECMO. There was an overall survival benefit when transferred to an ECMO center (63% vs 50%).

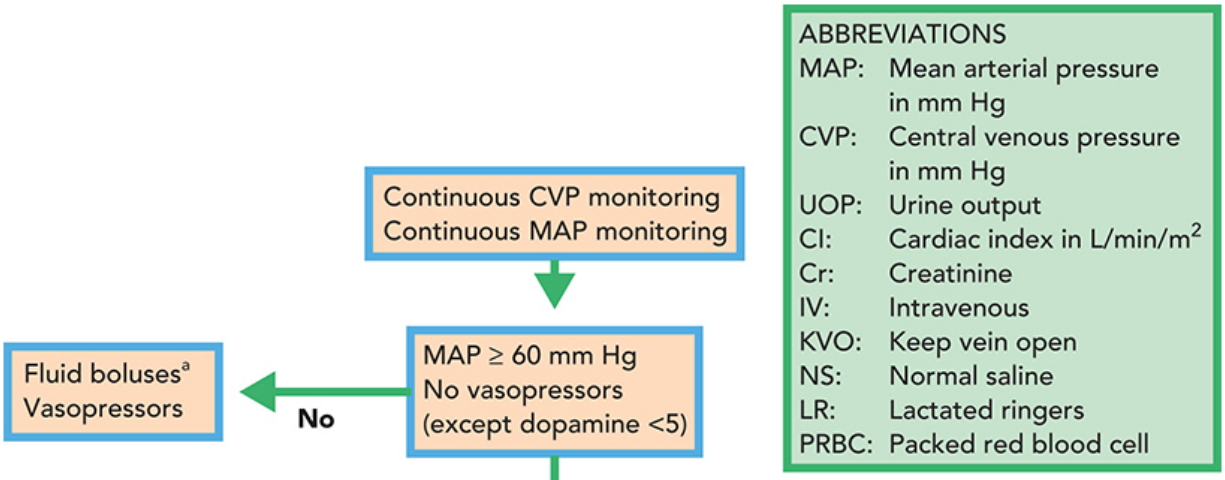
The larger EOLIA demonstrated a nonstatistically significant trend toward improved mortality in the ECMO arm. However, the study had an intention-to-treat design, and 28% of the patients in the control group crossed over to receive salvage ECMO therapy, of which 43% survived. Post-hoc Bayesian analyses suggest approximately 10% lower mortality in patients with severe ARDS that are eligible for and receive ECMO therapy.

There has been equipoise in the literature as to the benefit or harm of using glucocorticoids in ARDS. A prospective, randomized, double-blind, placebo-controlled clinical trial in 2007 by Meduri et al. of moderate-dose methylprednisolone (1 mg/kg for 2 weeks followed by a taper during 2 weeks) reported significantly reduced duration of mechanical ventilation, length of intensive care unit (ICU) stay, and ICU mortality in the group that received glucocorticoids. However, a larger study in 2006 by the ARDS Network showed no durable clinical benefit in patients treated with steroids within 7 days of ARDS onset and increased mortality in patients treated after 14 days after ARDS onset. More recently, a multicenter randomized, controlled trial with 277 patients investigated the use of dexamethasone in patients with moderate-to-severe ARDS (P/F < 200 mm Hg). Patients randomized to the intervention arm received 20 mg dexamethasone IV daily for 5 days followed by 10 mg dexamethasone IV daily for 5 days. Patients who received dexamethasone had more ventilator-free days (12.3 compared to 7.5) and decreased 60-day mortality (21% compared to 36%). Overall, the data supporting the use of moderate-dose steroids for ARDS are conflicting (Table 11.5). Clinicians should carefully weigh both the advantages and disadvantages of using corticosteroids in ARDS, especially when combined with neuromuscular blockers, due to the risk of critical illness myopathy and polyneuropathy. If a trial of steroids is administered, physiologic and radiologic parameters should improve substantially within 3 to 5 days; in patients that do not respond over this timeframe, it may be reasonable to discontinue the trial.

The injured lung during ARDS is also highly vulnerable to worsening pulmonary edema due to fluid overload. Historically, fluid

management during ARDS often emphasized the need to maintain intravascular volume to optimize hemodynamic performance, even at the risk of worsening pulmonary edema. While hemodynamic stability and organ perfusion need to be maintained, another trial by the ARDS Network from 2006 fluid and catheter treatment trial (FACTT) showed that minimizing pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP) can be safely performed without compromising systemic organ perfusion. In FACTT, patients in the “conservative” and “liberal” fluid arms were assigned to a treatment protocol every 4 hours based on four variables: (1) CVP or PAOP, (2) the presence or absence of shock, (3) the presence or absence of oliguria, and (4) the presence or absence of effective cardiac output (Algorithm 11.2). Treatment protocols consisted of combinations of IV fluids, diuretics, and/or inotropes. While there was no effect on mortality, patients treated with conservative fluid management arm experienced a decreased duration of mechanical ventilation and ICU stay.

ALGORITHM 11.2 **Fluid Management in Acute Lung Injury/Acute Respiratory Distress Syndrome**



	Average UOP <0.5 mL/kg/h		Average UOP ≥0.5 mL/kg/h	
	CI < 2.5 or cold, mottled extremities with capillary refill ≥2 s	CI ≥ 2.5 or no evidence of circulation impairment	CI < 2.5 or cold, mottled extremities with capillary refill ≥2 s	CI ≥ 2.5 or no evidence of circulation impairment
CVP > 13	1 Dobutamine [b] Furosemide	5 Furosemide	9 Dobutamine Furosemide	13 Furosemide
CVP 9-13	2 Dobutamine	6 Furosemide	10 Dobutamine	14 Furosemide
CVP 4-8	3 Fluid bolus[a]	7 Fluid bolus[a]	11 Fluid bolus[a]	15 Furosemide
CVP < 4	4 Fluid bolus[a]	8 Fluid bolus[a]	12 Fluid bolus[a]	16 KVO

For Cell # 1, 5, 6 furosemide 20 mg IV bolus, or IV infusion at 3 mg/h. **HOLD** if Cr > 3, or Cr 0-3 with labs consistent with renal failure, or vasopressor/fluid bolus in last 12 h.	Reassess in 1 h; double furosemide dose hourly until UOP > 0.5 mg/h or maximum of 24 mg/h or 160 mg bolus.	
For Cell # 9, 13, 14, 15 furosemide 20 mg IV bolus, or IV infusion at 3 mg/h. **HOLD** if Cr > 3, or Cr 0-3 with labs consistent with renal failure, or vasopressor/fluid bolus in last 12 h.	Reassess in 4 h; if still in cell where furosemide is indicated give same dose if UOP >3 mL/kg/h, double if ≤3 mL/kg/h, to a maximum of 24 mg/h or 160 mg bolus.t	
For Cell # 3, 4, 7, 8 give a NS, plasmalyte, or LR bolus of 15 mL/kg, 1 Unit PRBCs, or 25 g 25% albumin.	Reassess in 1 h.	Administer up to 3 boluses in 24 h if indicated by Cell #.
For Cell # 11, 12 give a NS, plasmalyte, or LR bolus of 15 mL/kg, 1 Unit PRBCs, or 25 g 25% albumin.	Reassess in 4 h.	Additional boluses at physician discretion
For Cell # 1, 2, 9, 10 dobutamine, start	Increase by 5 mcg/kg/min until CI >2.5	

For Cell # 1, 2, 9, 10 dobutamine, start at 5 mcg/kg/min. Increase by 5 mcg/kg/min until CI >2.5

[a]Fluid boluses should ideally only be administered to patients demonstrating fluid responsiveness using an objective dynamic measure to minimize the unnecessary use of crystalloid or oncotic solutions. Patients are considered fluid responsive if pulse pressure variability decreased to <13%, inferior vena cava distention index with respiration decreased to <18%, and the stroke volume index difference increased to >10%. Adapted from the 2006 FACTT trial, this complex algorithm may not be appropriate for all patients and in all clinical settings and should be used with physician discretion and judgment.

[b] If furosemide not available, can use bumetanide with a dose equivalency of 40:1 (Lasix 40 mg = bumetanide 1 mg).

Numerous studies have examined the long-term outcome of patients who survive ARDS. In one study, the average stay in the ICU from ARDS was 25 days. At discharge, patients had lost 18% of their body weight and had significant functional limitations. At 1 year, patients had persistent functional limitations due to muscle wasting and weakness. By 6 months to 1 year postrecovery, survivors exhibited normal or near-normal lung volume and spirometric measurements (defined as >80% of predicted), with most patients no longer requiring supplemental oxygen.

In summary, ARDS is a severe life-threatening form of pulmonary edema with characteristic clinical, radiologic, and physiologic consequences. Beyond treating the inciting event, current ARDS management centers on employing volume- and pressure-limited lung-protective ventilation, adopting conservative fluid management, and implementing prone position ventilation. Rescue therapies are reserved for patients who remain hypoxemic despite ventilator and fluid management. The use of specific rescue interventions such as ECMO are increasingly employed in certain high-risk populations (see Chapter 89, ECLS). At 1 year, survivors of ARDS may encounter some degree of functional disability due to muscle weakness and wasting, while lung function measurements are expected to approach normal values.

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Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med.* 2015;372(8):747-755.

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ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA.* 2012;307(23):2526-2533.

The Berlin Definition attempts to make the definition of ARDS more objective and offers severity categorization based on the degree of impaired oxygenation.

Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.

The American-European Consensus Conference on ARDS was established in 1992 between the American Thoracic Society and the European Society of Intensive Care Medicine. The goals of the Committee were to form a uniform definition of ALI and ARDS, better define the mechanism of acute lung injury, identify risk factors, prevalence, and outcomes, and to promote clinical study coordination.

Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA.* 2010;303(9):865-873.

Analysis of three trials comparing outcome in patients receiving higher PEEP versus lower PEEP levels. Overall, no difference in hospital survival was found. However, higher PEEP levels were associated with improved survival among the subgroup of patients with ARDS.

Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351(4):327-336.

The "ALVEOLI" trial was conducted by the ARDS Network at 23 affiliated centers. The trial compared mechanical ventilation with higher PEEP (mean 13.2 ± 3.5 cm H_2O) versus lower PEEP (mean 8.3 ± 3.2) when tidal volumes of 6 mL/kg PBW were used. The trial was stopped after 549 patients were enrolled when no significant difference was found between the two groups for death.

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Latent class analysis of the ARMA and ALVEOLI trial suggesting hyperinflammatory and hypoinflammatory subphenotypes of ARDS. The hyperinflammatory phenotype had increased mortality and fewer ventilator-free days when compared to the hypoinflammatory phenotype.

12 Acute Severe Asthma

Lauren Sattler and Kaharu Sumino

Asthma is a heterogeneous disease characterized by chronic airway inflammation, bronchoconstriction, and mucus hypersecretion. It is a common disorder affecting approximately 300 million worldwide and 24 million Americans with an estimated 1.6 million emergency department visits, 183,000 hospitalizations, and approximately 4,000 deaths per year in the United States. The economic impact of asthma is estimated to be $82 billion annually.

Recently, specific phenotypes of patients with near-fatal asthma have been identified through cluster analysis. Three clusters have been identified: (1) cluster 1: patients who are older, predominantly female, with very severe persistent asthma and frequent hospitalizations for asthma despite adherence to asthma treatment; (2) cluster 2: patients who smoke with intermediate asthma severity and frequently have psychiatric comorbidities and health care utilization often requiring mechanical ventilation; (3) cluster 3: patients who are younger, predominantly male, often with allergic sensitization, infrequent regular asthma care, and low adherence to asthma medications. This cluster analysis indicates heterogeneity in this patient population and underscores how different risk factors influence specific clusters of patients.

Acute severe asthma (formerly status asthmaticus) is recognized as a symptomatic exacerbation of asthma that is prolonged or unresponsive to routine bronchodilator therapy and often escalates to respiratory failure requiring admission to an intensive care unit, endotracheal intubation, or other rescue therapies. Approximately 10% of patients hospitalized with asthma are admitted to the intensive care unit, and 2% are intubated. Mortality rates range from 0.5% to 3% in hospitalized patients. Morbidity and mortality from asthma disproportionately affect the economically disadvantaged,

women, patients older than 35 years, and minorities, especially Black Americans. Risk factors for death from asthma are listed in Table 12.1.

TABLE 12.1 Risk Factors for Death From Asthma

Lower socioeconomic status
Female gender
African American
Smoking
“Labile asthma,” high degree of variability in peak expiratory flow
Blood eosinophilia
Poor perception of dyspnea: alexithymia, a psychological trait characterized by difficulty in perceiving and expressing emotions and body sensations
History of intubation for asthma
History of ICU admission for asthma
Two or more hospitalizations for asthma within the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma within past month
Use of more than two canisters per month of inhaled short-acting beta 2 agonists
Current use or recent withdrawal of oral corticosteroids
Poor perception of airflow obstruction
Comorbid cardiovascular disease
Sensitivity to alternaria

ED, emergency department; ICU, intensive care unit.

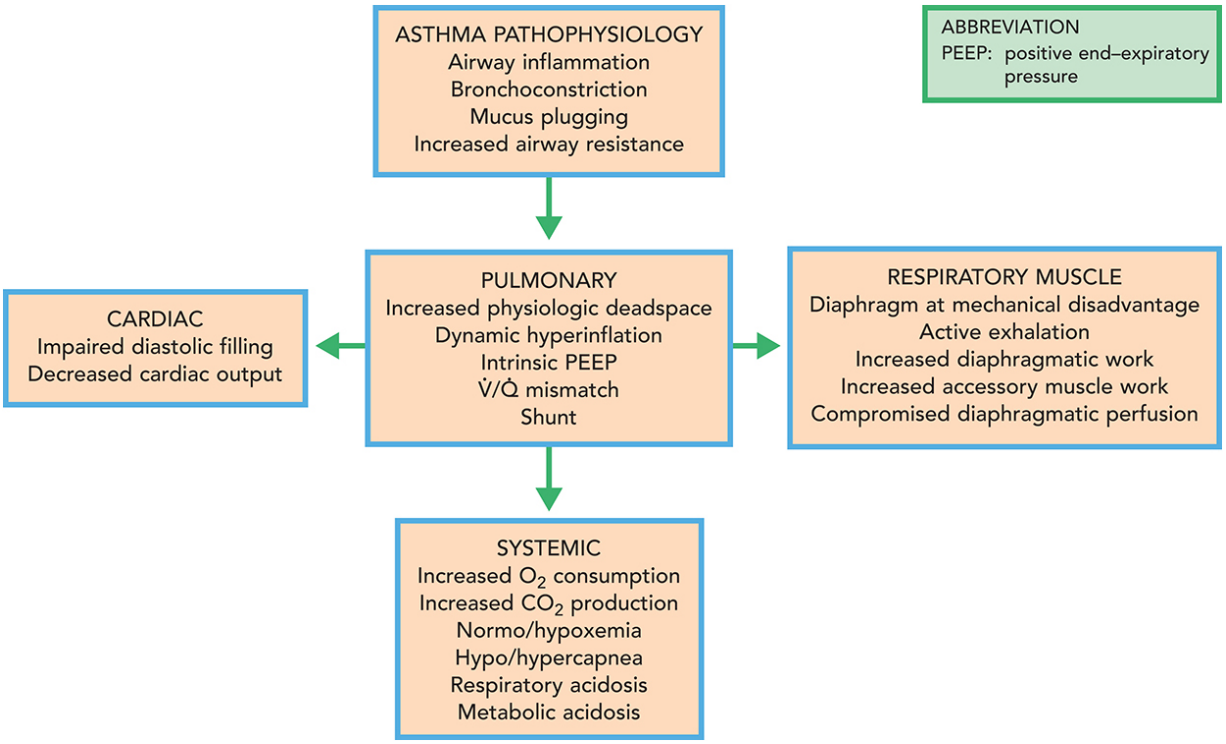
During acute episodes, patients present with dyspnea, cough, chest tightness, wheezing, and often report failure to respond to standard asthma therapies such as bronchodilators or corticosteroids. In severe asthma episodes, airway obstruction, respiratory muscle fatigue due to increased work of breathing, and altered $\dot{V}/\dot{Q}$ relationships can lead to respiratory failure due to hypercapnia and hypoxemia. This chapter will focus on the initial hospital and intensive care unit management, as well as ventilator strategies for patients with severe acute asthma.

The episodes of severe acute asthma may be rapid in onset (in a matter of hours) or, more typically, progress during several hours to days. The rapid onset of severe bronchospasm can be triggered by exposure to allergens, irritants, exercise, psychosocial stress, inhaled illicit drugs, or may also develop after exposure to aspirin, nonsteroidal anti-inflammatory drugs, or beta-blockers in susceptible individuals. More commonly, asthma episodes develop during several hours to days and may be triggered by viral or atypical infection. Airway obstruction in these cases is due to airway inflammation, bronchoconstriction, and mucus plugging.

These pathologic processes result in airway obstruction and expiratory airflow limitation. Insufficient expiratory time results in air trapping, dynamic hyperinflation (DHI), and persistent positive end–expiratory alveolar pressure, also referred to as *intrinsic positive end–expiratory pressure* (iPEEP). This alters lung mechanics by increasing work of breathing while simultaneously placing the diaphragm at a mechanical disadvantage. The increased work load placed on the respiratory muscles results in increased O_2 consumption and CO_2 production, and the increased intrathoracic pressure related to severe hyperinflation may ultimately result in cardiovascular collapse. During inspiration, there can be exaggerated right ventricular filling and paradoxical interventricular septal motion, resulting in impaired left ventricular filling. During expiration, the increased intrathoracic pressure impairs ventricular

diastolic filling, resulting in decreased cardiac output and compromised diaphragmatic blood flow, exacerbating metabolic acidosis and respiratory muscle fatigue. This downward spiral from the multiple pathophysiologic processes results in hypoxemic and hypercapnic respiratory failure (Algorithm 12.1).

ALGORITHM 12.1 Acute Severe Asthma Pathophysiology



Rapid evaluation of the patient presenting with acute severe asthma is essential, focusing on key points of their medical history, such as duration of symptoms, potential inciting exposures, medication use, and previous history of severe attacks. Patients should be questioned regarding the presence of symptoms suggestive of comorbid, complicating, or similarly presenting conditions such as upper airway obstruction, epiglottitis, and vocal cord dysfunction. Key historical and physical examination findings are listed in Table 12.2.

TABLE 12.2 Typical Physical Examination and Laboratory Findings in Asthma by Severity

Finding	Mild	Moderate	Severe	Respiratory Arrest Imminent
Breathless	Walking	Talking	At rest	
	Can lie down	Prefers sitting	Hunched forward	
Speaks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Respiratory rate	Increased	Increased	>30 breaths/min	
Accessory muscle use and retractions	Usually not	Usually	Usually	
Wheeze	Moderate, often end-expiratory	Loud	Usually loud	Absent
Pulse (beats/min)	<100	100-120	>120	Bradycardia (<60)
PEF	>80%	60%-80%	<60%	
Pa_{O_2}	Normal	>60 mm Hg	<60 mm Hg	
Pa_{CO_2}	<45 mm Hg	<45 mm Hg	>45 mm Hg	
Sa_{O_2}	>95%	91%-95%	<90%	

PEF, peak expiratory flow.

Treatments

STANDARD TREATMENT FOR ALL PATIENTS

Oxygen

- Supplemental oxygen to maintain Sa_{O_2} greater than 92%.

Inhaled Bronchodilators

- Beta 2 agonists administered via metered dose inhalers (MDIs) or nebulized bronchodilators mediate bronchodilation via cyclic adenosine monophosphate (c-AMP). Initial therapy is typically albuterol (2.5-5 mg) nebulized every 20 minutes (or four to eight puffs of MDI with spacer) within first hour. This should be continued every 1 to 4 hours as needed.
- Alternatively, albuterol may be given as a continuous nebulization at a dose of 10 to 15 mg during 1 hour with telemetry monitoring. A Cochrane review of 165 randomized controlled trials supports the use of continuous nebulization versus intermittent MDI in patients with severe acute asthma presenting to the emergency department to increase their pulmonary functions and reduce hospitalization.
- Levalbuterol (1.25 mg) nebulized every 20 minutes within the first hour, then every 1 to 4 hours as needed, can be used in place of albuterol. However, there is no data supporting its superiority over albuterol.
- Initial treatment should include ipratropium 0.5 mg nebulized every 20 minutes, given concomitantly with albuterol, as this has been shown to improve airflow limitation in acute asthma exacerbations in first 36 hours. Muscarinic antagonists act by impairing cyclic guanosine monophosphate (cGMP)–mediated bronchoconstriction.
- In the case of intubated patients, bronchodilators should be given via MDI (eg, albuterol along the inspiratory circuit or between a Y-

piece and the endotracheal tube).

- Long-acting beta 2 agonists (salmeterol, formoterol, vilanterol) are not indicated for the treatment of acute asthma. However, they may be continued as add-on therapy for hospitalized patient and in outpatient setting.
- The administration of intravenous beta 2 agonists is no more effective and potentially more toxic than delivery via aerosol and is therefore not recommended.

CORTICOSTEROIDS

- Corticosteroids decrease inflammation and upregulate beta-receptors. Administration of corticosteroids is critical for the resolution of severe asthma exacerbations; however, there is insufficient data available to provide specific guidance on dosage and routes of administration. In general, intravenous administration is reasonable for patients who are critically ill, and there is no additional benefit provided by a massive initial dose (eg, 500 mg methylprednisolone); therefore, a large initial dose (eg, 100-125 mg methylprednisolone intravenously once) is typically recommended.
- Subsequently, methylprednisolone at a dosage of 40 to 60 mg intravenously should be continued every 6 to12 hours (usually 2 mg/kg/d or less), or an equivalent oral dose can be given if there is no suspected impairment in gastrointestinal absorption.
- Consider tapering the dose after 36 to 48 hours, depending on the patient's clinical response.
- Of note, for patients with severe acute asthma secondary to COVID-19, administration of steroid therapy with dexamethasone (typically 6 mg intravenously daily) is likely sufficient to treat both disease states.

ADDITIONAL THERAPEUTIC CONSIDERATIONS

Antibiotics

- Not recommended routinely for uncomplicated asthma exacerbation, as most exacerbations are precipitated by viral infections.
- Justified if patients have fever, purulent sputum, or if there is evidence of pneumonia or bacterial sinusitis complicating the asthma exacerbation.

Magnesium

- IV administration of magnesium (2 g infused during 20 minutes) is relatively safe but does not appear to be more effective than standard therapy. There is no supporting data for its use beyond the initial dose in an emergency department setting. Magnesium is thought to antagonize calcium-mediated bronchoconstriction.
- Less data are available on the use of inhaled magnesium, but it may lead to a modest improvement in lung function during severe asthma exacerbations when used along with inhaled bronchodilators.

Methylxanthines

- Not recommended for initial treatment in acute asthma.
- Equivalent bronchodilator properties as beta 2 agonists but with increased potential of toxicity (tachyarrhythmia).

Epinephrine

- No proven advantage over inhaled bronchodilator therapy, but with added potential for toxicity, especially in hypoxemic patients.
- Consider in patients suspected to have an anaphylactic reaction or in those who are unable to cooperate with intensive inhaled bronchodilator treatment.
- Dosing: Administer 0.5 mg of a 1:1,000 dilution subcutaneously every 20 minutes, up to three dosages if needed.

Heliox

- The use of helium-oxygen ($He O_2$) mixtures in severe obstructive airway disease is based on the decreased density of heliox compared to air, which results in more laminar airflow rather than turbulent airflow.
- Use either 60%:40% or 70%:30% heliox (helium:oxygen) mixtures. Administration of heliox may be limited in patients with severe hypoxemia due to the necessarily lower fraction of inspired oxygen.
- Limited data suggest improved delivery of aerosolized bronchodilators (albuterol) when given with heliox rather than oxygen.
- The use of heliox in the mechanically ventilated patient should only be considered in those institutions that have significant experience and familiarity with its use because of potential technical complications regarding volume and pressure monitoring with standard ventilators.

VENTILATOR STRATEGIES

The goal of management in acute severe asthma is to unload the respiratory muscles, correct hypoxemia, provide adequate ventilation, and minimize DHI, while treating the underlying airway inflammation and bronchoconstriction.

Noninvasive Ventilation

- Use of noninvasive positive pressure ventilation (NIPPV) with either continuous positive airway pressure or bilevel positive airway pressure has increased dramatically in recent years. It may be considered suitable as the initial treatment for patients presenting to the emergency department with acute severe asthma, provided they are alert, cooperative, and capable of protecting their airways while tolerating a full face mask. Several studies have indicated that NIPPV reduces the work of breathing

during exacerbations of bronchospasm. Importantly, NIPPV may also prevent the need for intubation.

- Initial bilevel positive airway pressure settings should be selected and adjusted to meet the desired tidal volume or minute ventilation. In general, initial settings of inspiratory positive airway pressure (IPAP) at 10 and expiratory positive airway pressure (EPAP) of 5 are often sufficient. However, settings should be adjusted promptly to achieve patient comfort and compliance, reduce work of breathing (decreased respiratory rate, increased tidal volume), and avoid exceeding IPAP of 15 and EPAP of 5.
- Aerophagia with subsequent vomiting and aspiration are potential complications of NIPPV. Therefore, patients should be closely monitored and kept on a nothing by mouth status.
- Clinical reassessment after initiation of NIPPV should be performed shortly after initiation of NIPPV and pharmacologic treatment (within 30 minutes). Lack of improvement (ie, increased respiratory rate, worsening air movement, increased $Paco_2$) should prompt the clinician to the need for intubation and mechanical ventilation. Once deemed necessary, intubation should not be delayed.
- NIPPV is contraindicated in patients with decreased mental status and hemodynamic instability.

Invasive Ventilation

Ventilator strategies should concentrate on allowing adequate expiratory time to avoid DHI. This can typically be achieved by reducing respiratory rate (typically 10-14 breaths/min with an inspiratory to expiratory ratio of 1:3 or 1:4). If necessary, tidal volume may also be reduced to allow for complete exhalation. A permissive hypercapnia strategy should be employed, typically targeting a pH greater than 7.20. iPEEP should be monitored by performing an end-expiratory hold maneuver, with iPEEP being equal to total PEEP minus set PEEP (set on ventilator) (Figure 12.1). The goal should be to maintain iPEEP less than 20 cm H_2O while maintaining a plateau

pressure less than 30 cm H_2O. Increasing the flow rate (≥100 L/min) or square waveform has minimal impact on DHI once the minute ventilation has been limited. Mechanical ventilation with volume-controlled ventilation is preferable. Suggested initial settings are listed in Table 12.3.

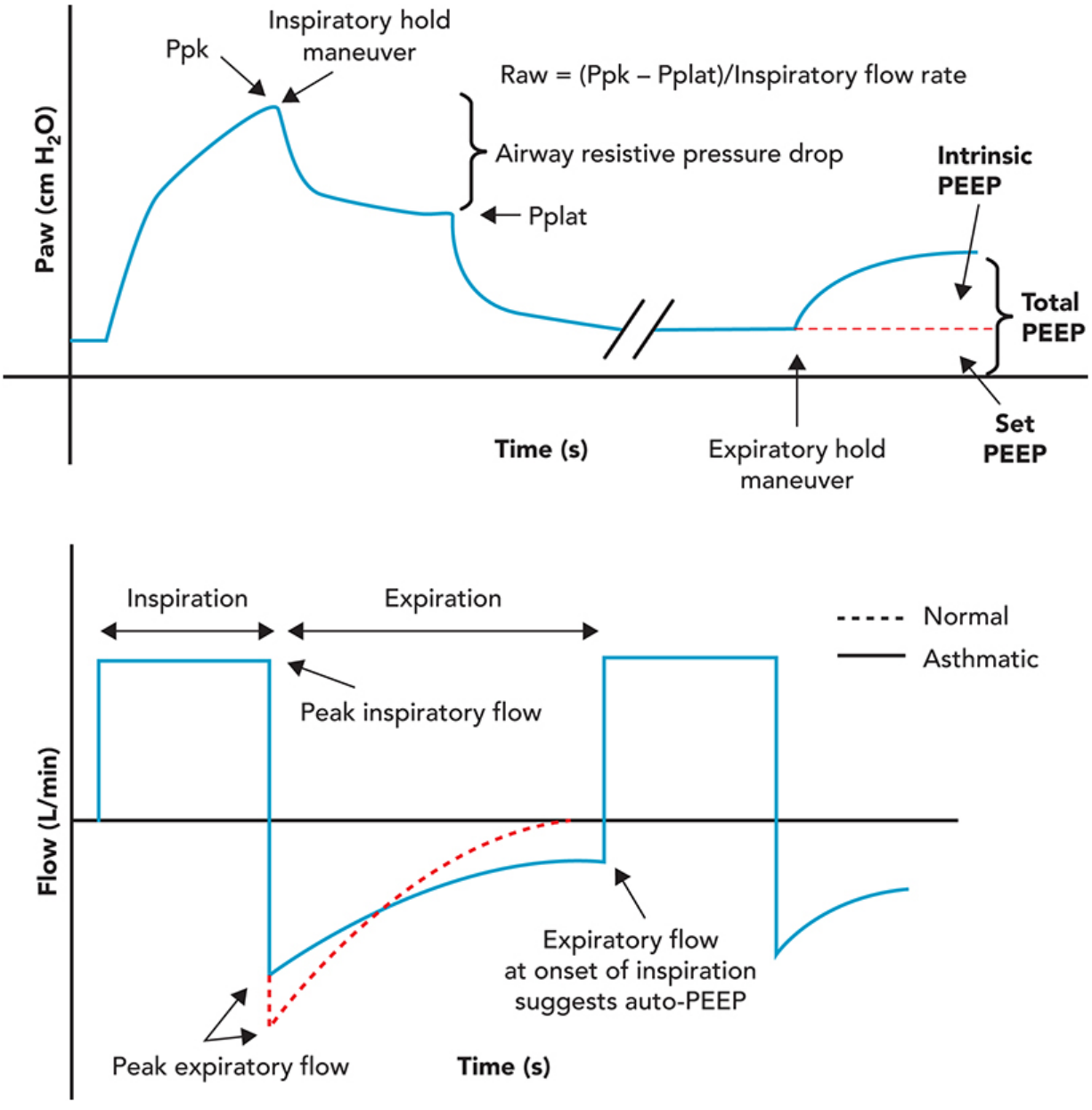


FIGURE 12.1 **Intrinsic positive end–expiratory pressure (PEEP)**. Ppk, peak pressure; Pplat, plateau pressure.

TABLE 12.3 Initial Ventilator Settings in Acute Severe Asthma

Parameter	Setting
Mode	Volume controlled
Minute ventilation	10 L
Tidal volume	6-8 mL/kg
Respiratory rate	10-14 breaths/min
Inspiratory flow rate	60-80 LPM
I:E	1:3 up to 1:5
PEEP	5 cm H_2O
F_{IO_2}	Titrate to keep Spo_2 > 90%

LPM, liters per minute, PEEP, positive end–expiratory pressure.

Intubation Considerations

Preparation for intubation is crucial and the procedure should be performed by a skilled intensivist or anesthesiologist. Some studies have demonstrated increased mortality with smaller endotracheal tube size; therefore, patients should be intubated with a size 8.0 mm tube. In addition to decreasing airway resistance, a large tube size allows adequate room for suctioning and bronchoscopy, if needed. Complications include arrhythmias, laryngospasm, aspiration, and pneumothorax due to excessive bagging. Propofol, etomidate, and ketamine are appropriate induction agents using rapid sequence induction. Hypotension during or postintubation is common in severe acute asthma because of multiple factors, including the application of positive pressure throughout the respiratory cycle in patients with

pre-existing DHI and iPEEP, hypovolemia, and sedation. It should be managed with sedatives and liberal intravenous fluids (IVFs) as well as the aforementioned ventilator strategies to minimize DHI. If needed, with close monitoring of Spo_2, the patient can be disconnected from the ventilator circuit to allow adequate exhalation of trapped gas and decrease intrathoracic pressure.

Other Considerations

A combination of propofol (or benzodiazepine) with fentanyl should be considered for sedation to minimize patient-ventilator dyssynchrony and to enforce controlled hypoventilation. Ketamine can be considered for sedation due to its anesthetic as well as bronchodilatory properties, although there is minimal data available to support routine use. Neuromuscular blockade should be considered in patients with status asthmaticus on mechanical ventilation who demonstrate considerable patient-ventilator dyssynchrony with unacceptably high plateau pressures and iPEEP despite adequate sedation and analgesia. Neuromuscular blocking agents should be given as intermittent boluses with neuromuscular (train of four) monitoring. Administration of neuromuscular blocking agents as continuous infusions should be avoided because of the increased risk of myopathy associated with concurrent corticosteroid use. For refractory cases, inhaled anesthetics (sevoflurane, isoflurane, and halothane) have been used.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) can be considered as a salvage therapy in acute severe asthma that is refractory to usual care, such as bronchodilators, corticosteroids, and mechanical ventilation. While available data remain limited, retrospective analysis has demonstrated a potential mortality benefit associated with use of ECMO as a salvage therapy for hypoxemic or hypercapnic respiratory failure in acute severe asthma. Prospective

clinical trials are needed to confirm these findings and further define the role of ECMO in acute severe asthma.

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13 Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Andrew T. Peters and James Krings

Chronic obstructive pulmonary disease (COPD) is the third largest cause of death worldwide. The estimated global prevalence of COPD is 10.3%, which is expected to increase further in both high- and low-income countries due to population aging and the rising prevalence of tobacco smoking, respectively. Worldwide, there were approximately 3 million deaths attributed to COPD in 2017. In the United States, COPD was the sixth leading cause of death in 2020, and health care costs attributed to COPD are projected to reach $40 billion per year over the next two decades. The majority of these costs are due to acute exacerbations of COPD (AECOPD).

COPD is defined by chronic small-airway inflammation (bronchitis) and alveolar destruction (emphysema) that both contribute to expiratory airflow obstruction. Symptoms include chronic dyspnea and cough with or without sputum production. The diagnosis is made by spirometry, demonstrating a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <70%.

The severity of COPD can be stratified by spirometry, validated questionnaires for symptom assessment, and the frequency of exacerbations. This is illustrated by the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD classification model depicted in Figure 13.1. From a critical care perspective, one notable feature of this latest COPD paradigm is that even a single AECOPD hospitalization automatically places a patient in the highest severity category (group E), which reflects the clinical significance of AECOPD as a negative prognostic sign.

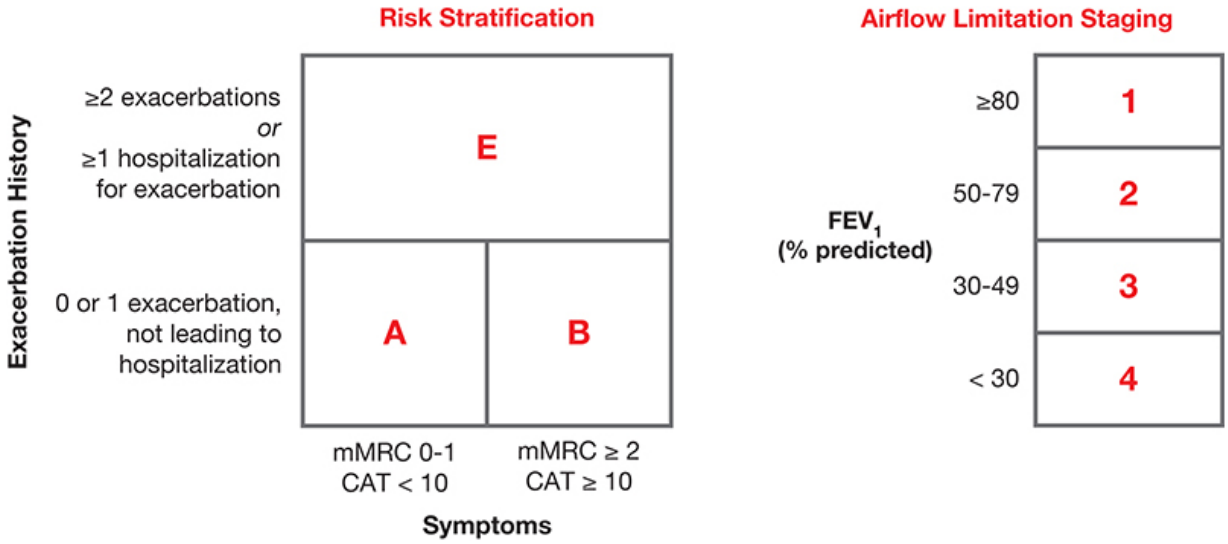


FIGURE 13.1 **Chronic obstructive pulmonary disease (COPD) classification model** (derived from the Global Initiative for Chronic Obstructive Lung Disease—GOLD 2023 Report). CAT, COPD Assessment Test; FEV_1, forced expiratory volume in one second; mMRC, Modified Medical Research Council.

Diagnosis

Though AECOPD is commonly triggered by airway infections or environmental exposures, about one-third of exacerbations have no identified trigger.

AECOPD is defined by acute worsening of dyspnea, cough, and/or sputum production in a patient with underlying COPD. AECOPD is a purely clinical diagnosis, so it is imperative to exclude alternate diagnoses before concluding AECOPD is the etiology of a patient's symptoms. In particular, pneumonia, heart failure, and pulmonary embolism (PE) commonly mimic AECOPD symptoms. Suggested diagnostic evaluation for suspected AECOPD is summarized in Table 13.1.

TABLE 13.1 **Initial Evaluation of Suspected AECOPD**

Clinical	• Increased cough, dyspnea, and/or sputum production?

history	• Recent sick contacts and/or environmental exposures? • Prior COPD exacerbations, hospitalizations, and/or ICU admissions?
Physical examination	• Vital signs: tachypnea, tachycardia • Wheezing • Accessory respiratory muscle use • Prolonged expiratory phase
Objective testing	• Complete blood count and basic metabolic panel • Chest radiograph • Arterial or venous blood gas • Respiratory viral testing[a] • Sputum culture (if able to produce a high-quality sample) • Review medical records for prior spirometry if available. *Also consider:* • CTPA if PE remains in the differential diagnosis • Echocardiogram if HF, pulmonary hypertension, or PE remains in the differential diagnosis

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; CTPA, computed tomography pulmonary angiography; HF, heart failure; ICU, intensive care unit; PE, pulmonary embolism.
[a]Specific viruses to be tested will depend on locally available assays and epidemiology. At a minimum, influenza and SARS-CoV-2 polymerase chain reaction (PCR) testing should be performed, given the availability of specific therapies for these viral etiologies.

On physical examination, most patients with AECOPD have wheezing, but this association is not absolute. Importantly, patients with severe AECOPD can have too little air movement to generate audible wheezing; in such cases, the only findings on chest auscultation will be diminished breath sounds, tachypnea, and/or a prolonged expiratory phase. Conversely, pulmonary edema can also generate wheezing in the absence of bronchospasm.

Laboratory values in AECOPD may include a reactive leukocytosis, though this is nonspecific. Sputum cultures and respiratory viral testing may reveal a specific pathogenic trigger.

Arterial blood gas (ABG) testing often demonstrates hypercapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] >50 mm Hg) and/or hypoxemia (arterial partial pressure of oxygen [PaO_2] <60 mm Hg), which can be useful to guide therapeutic decisions, as discussed later.

In uncomplicated AECOPD, chest radiographs are typically normal or demonstrate only chronic findings, such as hyperinflation. However, chest radiographs are crucial to rule out other causes of acute dyspnea, such as pneumonia, pulmonary edema, and pneumothorax. Clinicians should also have a low threshold to consider PE, which complicates 5% to 15% of AECOPD cases and is often overlooked. CT pulmonary angiography (CTPA) is the preferred diagnostic test for PE in this context; lung ventilation-perfusion scans can be difficult to interpret, given baseline ventilation abnormalities associated with COPD. A bedside ultrasound, by an adequately trained operator, can be useful to identify deep vein thrombosis and/or right ventricular dysfunction as a proxy for PE when CTPA is unavailable and to identify left ventricular heart failure as an alternative cause of dyspnea.

Management

INHALED BRONCHODILATORS

Short-acting inhaled bronchodilators are a mainstay in the treatment of AECOPD and appear to improve symptoms and FEV_1; however, high-quality evidence supporting their use is surprisingly limited. First-line therapy for AECOPD should be a short-acting beta2-adrenergic receptor agonist (SABA; eg, albuterol or levalbuterol), either alone or in combination with a short-acting muscarinic antagonist (SAMA; eg, ipratropium). Metered-dose inhalers (MDI) and nebulizers are generally equally effective for administering short-acting bronchodilators. However, patients who are acutely ill may have difficulty coordinating breathing with actuations or generating

forceful inspiratory effort, and, thus may derive more benefit from nebulized therapies.

Inhaled short-acting bronchodilators are generally safe and well tolerated. SABAs occasionally cause tachycardia, palpitations, tremulousness, and/or lactic acidemia; however, these effects are rarely dangerous and resolve quickly with a reduction in the medication dose or frequency. Systemic bronchodilators, such as intravenous methylxanthines (ie, theophylline), are not recommended due to significant adverse effects and no advantage in efficacy over inhaled agents.

Whether patients should continue taking their long-acting medications while acutely ill has not been specifically studied. However, patients taking long-acting inhaled bronchodilators and/or inhaled corticosteroids prior to admission can generally continue these agents during an acute exacerbation.

CORTICOSTEROIDS

Systemic corticosteroid treatment for AECOPD has demonstrated benefits including quicker recovery time, decreased risk of treatment failure, decreased length of hospitalization, and improvement in FEV_1. Oral and parenteral corticosteroids are considered equally effective. The optimal duration of systemic steroid treatment is not clearly established. One randomized controlled trial (Reduction in the Use of Corticosteroids in Exacerbated [REDUCE] COPD trial) demonstrated a treatment duration of 5 days to be noninferior to 14 days. In general, given the potential adverse effects of corticosteroids ranging from hyperglycemia and muscle weakness to increased risk of pneumonia, the lowest effective dose and duration of corticosteroids should be prescribed.

The available evidence suggests that a 5-day course of prednisone 40 mg daily (or equivalent corticosteroid dose) is adequate for most patients with AECOPD, including in the intensive care unit (ICU). However, dosing and duration may be individualized based on exacerbation severity, risk of side effects, and response to therapy. Despite a paucity of data, some clinicians choose higher

initial corticosteroid doses and/or longer courses in a minority of patients with especially severe or recurrent presentations. For example, patients who require mechanical ventilation or have evidence of persistent severe bronchospasm on exam sometimes receive initial corticosteroid doses on the order of 125 mg methylprednisolone daily, tapered gradually over 10 to 14 days. Such higher-dose steroid regimens are reasonable for clinicians to consider on an individualized basis, but should not be employed as a general practice.

ANTIMICROBIALS

Multiple studies have demonstrated that antibiotics in appropriately selected patients with AECOPD reduce treatment failure, reduce sputum production, and may reduce mortality. Furthermore, these benefits are most significant in the sickest patients, particularly those requiring ICU care.

Bacteria commonly implicated in airway mucosal infection causing AECOPD include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus* species; *Pseudomonas aeruginosa* is also increasingly seen in patients with advanced COPD and/or recent hospitalizations. However, AECOPD is also frequently triggered by respiratory viruses and by noninfectious, environmental irritants.

Numerous antibiotic classes have shown benefit in the treatment of AECOPD including macrolides, penicillins, tetracyclines, quinolones, and trimethoprim-sulfamethoxazole. Traditionally, macrolides (eg, azithromycin) are a popular choice for AECOPD as they are well tolerated and theoretically provide benefit via a direct anti-inflammatory mechanism in addition to their antibacterial properties. There is no high-quality evidence suggesting that any one of the aforementioned antibiotic classes is superior to the others in AECOPD. In the absence of such evidence, we suggest an individualized antibiotic selection approach that balances risk stratification with antibiotic stewardship. A high-quality sputum sample, if collected, can also help guide antibiotic selection.

One reasonable approach when considering antibiotics for AECOPD is to stratify patients based on the severity of their exacerbation and their probability for *P. aeruginosa* colonization. For ICU patients with AECOPD and no significant risk factors for a poor outcome (ie, absence of baseline FEV_1 <50% predicted, frequent exacerbations [≥2 exacerbations annually], hospitalization in the prior 3 months, need for mechanical ventilation, and/or chronic baseline need for supplemental oxygen), oral treatment with a macrolide, doxycycline, or amoxicillin/clavulanate is likely reasonable. For higher-risk patients, we recommend a third-generation cephalosporin (eg, ceftriaxone) or, less preferentially, a respiratory fluoroquinolone.

All patients receiving antibiotics for AECOPD should be carefully risk stratified for *P. aeruginosa* airway colonization (eg, presence of bronchiectasis, recent exposure to intravenous antibiotics, chronic treatment with oral steroids, and/or the presence of previous respiratory cultures with *P. aeruginosa*) and should be treated with an antipseudomonal agent if risk factors exist. Antimicrobial options include antipseudomonal penicillins, cephalosporins with antipseudomonal activity, fluoroquinolones, monobactams, and carbapenems.

The optimal duration of antibiotic therapy is not clearly established, but most antibiotic courses are 5 to 7 days. Three days is likely sufficient when treating with macrolides. Example dosing schedules are shown in Table 13.2.

TABLE 13.2 Medical Therapies for AECOPD

Category	Medication and Dosing[a]
Bronchodilators	Albuterol 180 mcg MDI or 2.5-5 mg nebulized every 4-6 h, *with or without* Ipratropium bromide 18-36 mcg MDI or 0.5 mg nebulized every 4-6 h Decrease frequency as the condition improves.

Category	Medication and Dosing[a]
Corticosteroids	Prednisone 40 mg po daily for 5 d recommended for most patients For patients requiring mechanical ventilation and/or with prolonged severe bronchospasm, consider initial dosing of methylprednisolone 125 mg IV daily for 1-3 d followed by prednisone taper over 10-14 d.
Antibiotics (low risk of decompensation)	Azithromycin 500 mg po daily for 3 d, or 500 mg on the first day, then 250 mg daily for 4 d Amoxicillin-clavulanate[b] 875-125 mg po every 12 h for 5 d Doxycycline 100 mg po every 12 h for 5 d
Antibiotics (high risk of decompensation)	Ceftriaxone 1-2 g IV every 24 h for 5-7 d Levofloxacin[b] 500-750 mg po or IV daily for 5-7 d
Antibiotics (high risk of *Pseudomonas* airway colonization)	Levofloxacin[b] 750 mg po or IV daily Cefepime[b] 2 g IV every 8 h Piperacillin-tazobactam[b] 4.5 g IV every 6 h

AECOPD, acute exacerbations of chronic obstructive pulmonary disease; IV, intravenously; MDI, metered-dose inhalers; po, orally.

[a]The sample regimens listed here are not exhaustive; in particular, other corticosteroid and antibiotic regimens may be reasonable depending on patient factors. Refer to the “Antimicrobials” section of the text for information on risk factors for *Pseudomonas aeruginosa* airway colonization and severe AECOPD.

[b]These antibiotics require dose adjustment for renal impairment; the doses listed in the table assume normal renal function.

Lastly, patients requiring ICU care for AECOPD secondary to influenza or COVID-19 infection should receive antiviral therapy. For influenza, oseltamivir is recommended in this patient population regardless of the duration since symptom onset; notably, zanamivir is contraindicated in patients with AECOPD due to the risk of worsening bronchospasm. For COVID-19, remdesivir is currently

first-line therapy in hospitalized patients (along with dexamethasone if hypoxemic), though this recommendation may change with future evidence. Refer to the Chapter 38 (Community-Acquired Pneumonia) and Chapter 39 (Nosocomial Pneumonia) of this text for further details on the choice of antimicrobials.

NONRECOMMENDED THERAPIES

Mucolytic agents (eg, *N*-acetylcysteine), methylxanthine bronchodilators (eg, theophylline), and chest physiotherapy have all been shown to be nonbeneficial in the treatment of AECOPD; in addition, the latter two may be harmful. Though employed historically, these treatments should not be used for AECOPD based on current evidence.

Studies have shown equivocal improvement in FEV_1 from administration of magnesium sulfate in AECOPD; consequently, some clinicians routinely use intravenous magnesium in AECOPD, especially for severe presentations. This practice is probably safe, but its benefits are not clearly established, and it is not recommended by major society guidelines.

OXYGEN AND NONINVASIVE VENTILATION

Patients who are hypoxemic with AECOPD should receive supplemental oxygen titrated to a goal arterial oxygen saturation (Sa_{O_2}) of 88% to 92% or Pa_{O_2} of 60 to 70 mm Hg. Achieving Sa_{O_2} greater than 92% is unnecessary and potentially harmful as it may precipitate worsening hypercapnia and ventilation-perfusion mismatching.

Noninvasive positive pressure ventilation (NPPV) is indicated for patients with AECOPD who have acute respiratory acidosis (Pa_{CO_2} >45 mm Hg *and* arterial pH <7.35) and/or clinical signs of increased work of breathing (such as use of accessory respiratory muscles or intercostal retractions). Use of NPPV in AECOPD has been shown to confer multiple benefits including improvement in respiratory

acidosis, improvement in symptoms, lower rates of endotracheal intubation, and decreased mortality.

Typical initial NPPV settings for patients with AECOPD utilize the bilevel positive airway pressure (BiPAP) mode with inspiratory positive airway pressure (IPAP) of 10 to 15 mm Hg and expiratory positive airway pressure (EPAP) of 5 to 8 mm Hg. Patients already on long-term nocturnal noninvasive ventilation (NIV) prior to admission usually need a higher driving pressure (difference between IPAP and EPAP) during AECOPD than at their baseline settings.

Frequent clinical reassessment and serial blood gas measurements are critical to assess response to NIV therapy and guide adjustment of settings. Therapeutic success is reflected by improvement in tachypnea, decreased work of breathing, normalization of arterial pH, and decrease in $Paco_2$. However, care should be taken to avoid hyperventilation (ie, do not lower $Paco_2$ below the patient's baseline and/or raise arterial pH >7.40).

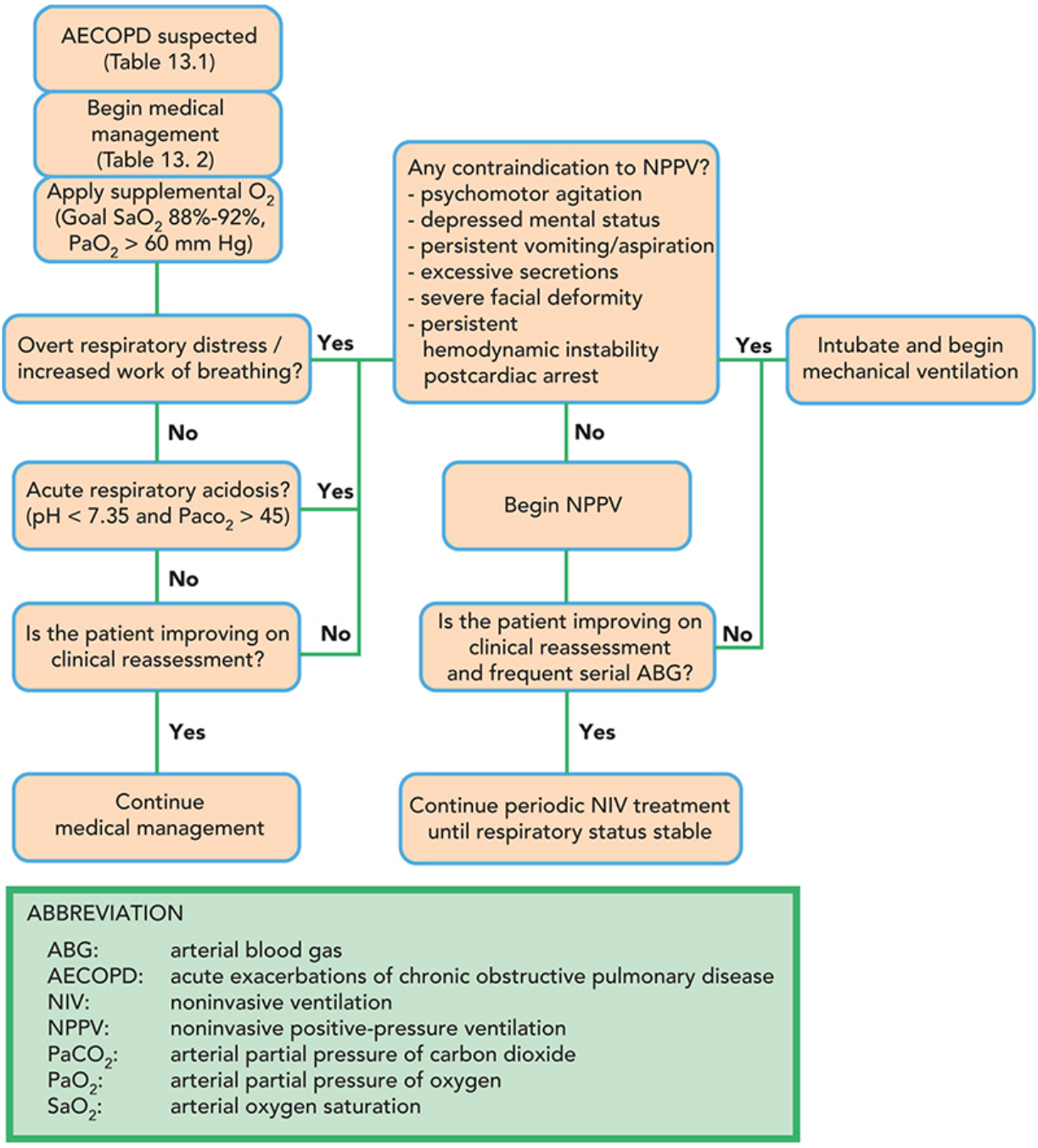
Initial treatment of acute respiratory failure in AECOPD should generally be with NPPV rather than invasive mechanical ventilation (IMV) unless there is a contraindication to NPPV. Such contraindications include psychomotor agitation, severely depressed consciousness, large-volume emesis or aspiration, inability to manage respiratory secretions, severe facial deformity, persistent hemodynamic instability, cardiopulmonary arrest, and any other factor that precludes maintaining a tightly sealed face mask for at least several hours.

High-flow nasal oxygen therapy (HFNT), a heated and humidified air-oxygen delivery system that provides flow rates up to 60 L/min, should not generally be used in AECOPD. Studies of HFNT in AECOPD suggest that it may improve symptoms but, in contrast to NIV, it has not been shown to reduce the risk of endotracheal intubation and mortality.

INVASIVE MECHANICAL VENTILATION

Patients with AECOPD and acute respiratory failure that worsens despite an adequate trial of NPPV, or who have a contraindication to NPPV, should promptly undergo endotracheal intubation and IMV. A schematic approach to evaluating the need for NPPV or IMV in AECOPD is depicted in Algorithm 13.1.

ALGORITHM 13.1 **Ventilatory Support in AECOPD**


AECOPD suspected (Table 13.1)
Begin medical management (Table 13. 2)
Apply supplemental O_2 (Goal SaO_2 88%-92%, PaO_2 > 60 mm Hg)
Overt respiratory distress / increased work of breathing?
Yes
No
Acute respiratory acidosis? (pH < 7.35 and $Paco_2$ > 45)
Yes
No
Is the patient improving on clinical reassessment?
No
Yes
Continue medical management
Any contraindication to NPPV?
- psychomotor agitation
- depressed mental status
- persistent vomiting/aspiration
- excessive secretions
- severe facial deformity
- persistent hemodynamic instability postcardiac arrest
Yes
No
Intubate and begin mechanical ventilation
Begin NPPV
Is the patient improving on clinical reassessment and frequent serial ABG?
No
Yes
Continue periodic NIV treatment until respiratory status stable
ABBREVIATION
ABG: arterial blood gas
AECOPD: acute exacerbations of chronic obstructive pulmonary disease
NIV: noninvasive ventilation
NPPV: noninvasive positive-pressure ventilation
$PaCO_2$: arterial partial pressure of carbon dioxide
PaO_2: arterial partial pressure of oxygen
SaO_2: arterial oxygen saturation

Initial ventilator settings in AECOPD commonly utilize the assist-control volume control mode with a respiratory rate between 12 and 14 breaths per minute, tidal volume of 6 to 8 cc/kg ideal body weight, and positive end-expiratory pressure (PEEP) of 5 cm H_2O. FIO_2 should be the lowest necessary to achieve SaO_2 between 88% and 92% or PaO_2 60 to 70 mm Hg. As with NPPV, patients should not be

ventilated to a “normal” $PaCO_2$, but rather to a normal or slightly acidemic pH near their *baseline* $PaCO_2$. Adequate (but not excessive) sedation should be provided to allow for ventilator synchrony and patient comfort.

Due to the expiratory airflow obstruction characteristic of their disease, patients with AECOPD require a prolonged expiratory time, ideally with an inspiratory-to-expiratory (I:E) ratio of at least 1:4. Maneuvers to give adequate expiratory time include reducing respiratory rate and/or tidal volume (to the extent possible without compromising ventilation), and increasing inspiratory flow rate in a volume control mode (up to 75-90 L/min) or decreasing inspiratory time in a pressure control mode.

Mechanically ventilated patients with AECOPD must be monitored for autoPEEP (also known as intrinsic PEEP), a phenomenon that results from air trapping due to excessive tidal volumes and/or inadequate expiratory time. AutoPEEP is deleterious because it leads to increased intrathoracic volume and pressure that can cause barotrauma and limits venous blood return, as well as causing increased work required to trigger a ventilator breath. In severe cases, autoPEEP can cause systemic hypotension and cardiovascular collapse. AutoPEEP is best detected and measured using the expiratory pause maneuver on the ventilator.

If significant autoPEEP is present, ventilator settings should be adjusted to prolong expiratory time as described earlier. In addition, patients with increased work of breathing may need a judicious increase in extrinsic PEEP to reduce autoPEEP. Lastly, if persistent hypotension is attributed to autoPEEP, clinicians should briefly disconnect the patient from the ventilator circuit, perform slow manual chest wall compression in order to expel trapped air, and then reconnect the ventilator. This rescue maneuver restores neutral intrathoracic pressure and normal venous return.

Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease After Hospital

Discharge

Hospitalization for AECOPD strongly predicts future hospitalization and mortality. Clinicians should recognize ICU admission for AECOPD as a landmark event with deep health implications that extend beyond the patient's ICU stay and as an opportunity to optimize the patient's long-term COPD management.

MEDICAL THERAPIES

All patients admitted for AECOPD should, prior to discharge, begin appropriate long-acting maintenance inhalers to improve symptoms and reduce the risk of future exacerbations.

Current high-quality evidence indicates that for patients with at least one severe COPD exacerbation in the past year, "triple inhaler therapy" (ie, the combination of a long-acting muscarinic antagonist [LAMA], long-acting beta2-agonist [LABA], and inhaled corticosteroid [ICS]) is superior to other long-acting inhaler regimens at preventing future exacerbations. Although "triple inhaler therapy" initiation during an index hospitalization for AECOPD has not been specifically studied, the known benefits of this inhaler strategy suggest that it would be the preferred long-term outpatient inhaler regimen after hospital discharge for an AECOPD that requires critical care management.

On this basis, we suggest that patients with AECOPD requiring ICU admission be discharged on a LAMA-LABA-ICS combination. For patients with a history of recurrent pneumonia, mycobacterial infection, and/or financial barriers to triple therapy, a LAMA-LABA combination is a reasonable alternative. In contrast, a LABA-ICS combination alone should not generally be used for patients with COPD.

Prior to discharge, patients who experienced an AECOPD should be counseled on inhaler technique and, if necessary, on smoking cessation. Influenza and pneumococcal vaccinations should be updated if needed. Antibiotics and systemic corticosteroids begun in

the ICU may be continued after discharge to complete a short course, as discussed earlier.

Selected patients with severe COPD and frequent exacerbations despite optimal inhaler therapy may be considered for long-term azithromycin and/or phosphodiesterase-4 inhibitor treatment (ie, roflumilast). However, these therapies are generally initiated in the outpatient setting.

OXYGEN AND NOCTURNAL NONINVASIVE VENTILATION

Patients who were hypoxemic during admission should undergo resting and walking oxygen evaluation 24 to 48 hours before discharge to evaluate for home oxygen needs.

Patients with chronic hypercapnic respiratory failure due to COPD may warrant long-term nocturnal NPPV, with benefits including improved symptoms and lower future hospitalization rates. AECOPD hospitalizations are an important opportunity to identify the need for nocturnal NPPV, but the optimal timing to begin NPPV after an AECOPD remains unclear. Available evidence suggests it is safe to delay assessment for NPPV until 2 to 4 weeks after resolution of AECOPD. However, many clinicians choose to initiate long-term NPPV during the index AECOPD hospitalization, especially for patients with severe chronic hypercapnia and/or barriers to timely outpatient follow-up.

Patients with COPD and known, or suspected, comorbid obstructive sleep apnea (OSA) should undergo polysomnography with positive airway pressure titration to confirm the indication for nocturnal NPPV and determine optimal settings. Patients with severe COPD without OSA qualify for nocturnal NPPV by United States Centers for Medicare & Medicaid Services guidelines if they have a daytime $Paco_2$ >52 mm Hg *and* sustained desaturation to Sao_2 <88% for ≥5 cumulative minutes while using their usual supplemental oxygen while asleep. In patients without OSA, the main physiologic goal of nocturnal NPPV is the gradual normalization of $Paco_2$.

PULMONARY REHABILITATION

Pulmonary rehabilitation is a multifaceted intervention that includes 8 to 12 weeks of exercise training and health behavior coaching. Pulmonary rehabilitation has been shown to improve symptoms, exercise capacity, and—in some studies—mortality after AECOPD. Patients with at least moderate underlying COPD should begin pulmonary rehabilitation within 4 weeks of hospital discharge for AECOPD.

PALLIATIVE AND END-OF-LIFE CARE

The negative prognostic significance of even a single hospitalization for AECOPD is often underrecognized. One-year mortality after hospitalization for AECOPD is 20% to 30%, with outcomes that are even worse for those who require ICU care. Moreover, patients with COPD often have high symptom burdens (including dyspnea, cough, fatigue, depression, anxiety, and insomnia) despite optimal disease-directed medical therapy. Palliative care can provide additional symptomatic relief, support for complex decision-making, and assistance with end-of-life planning—which is most valuable when initiated well before the end of life. However, palliative care is markedly underutilized in COPD.

ICU hospitalization for AECOPD should prompt—at least consideration for—inpatient palliative care consultation or outpatient referral, especially for patients with severe baseline symptoms and/or multiple previous exacerbations. During hospitalization, the ICU team should explore patients' care preferences, including limitations on life-sustaining treatment such as IMV. For patients with especially severe COPD and/or life-limiting comorbidities judged to confer a life expectancy of 6 months or less, hospice referral should be offered if in line with the patient and family's goals.

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14 Sleep-Disordered Breathing in the Intensive Care Unit

Rutwik Patel and Tonya D. Russell

Sleep has a range of effects on respiratory physiology in healthy patients, as outlined in Table 14.1. In patients with underlying comorbidities, such as severe chronic obstructive pulmonary disease or neuromuscular disease, these effects on respiratory physiology can lead to compromise of the patient's cardiopulmonary status. In addition, there are sleep-related breathing disorders that can lead to respiratory failure in which the main pathophysiology occurs during sleep, such as obstructive sleep apnea (OSA), central sleep apnea (CSA), and obesity hypoventilation.

TABLE 14.1 Effects of Sleep on Respiratory Physiology

Decreased hypoxic ventilatory response
Decreased hypercapnic ventilatory response
Increased muscle hypotonia
Increased airway resistance
Increased arousal threshold from events related to increased airway resistance (NREM > REM)

NREM, nonrapid eye movement; REM, rapid eye movement.

Apneic events during sleep can either be obstructive or central in nature. Obstructive events are associated with ongoing respiratory effort, while there is minimal to no respiratory effort present with central apneas. OSA occurs when there is narrowing or complete

obstruction of the upper airway during sleep due to excessive soft tissue or structural abnormalities, resulting in limitation or cessation of airflow, which can be associated with arousals or oxygen desaturations. OSA is associated with an increased risk of excessive daytime somnolence, hypertension, atrial fibrillation, stroke, heart failure, and all-cause mortality. The severity of OSA can be quantified by the number of events per hour of sleep (apnea-hypopnea index) or by the severity of sleepiness, as shown in Table 14.2.

TABLE 14.2 Severity of Obstructive Sleep Apnea

Severity	AHI[a]	Level of Impairment[b]
Mild	5-15	Sedentary activities requiring minimal attention (ie, watching television, reading, passenger in a car)
Moderate	15-30	Activities requiring some attention (ie, meetings, concerts)
Severe	>30	Activities requiring active attention (ie, conversation, eating, driving)

[a]AHI (apnea-hypopnea index), number of apneas and hypopneas per hour of sleep; apnea is defined as cessation of airflow; hypopnea is defined as >30% reduction in airflow associated with a 3% oxygen desaturation or arousal; all events must be at least 10 seconds.
[b]Extent of daytime somnolence.

The prevalence of OSA-hypopnea syndrome (OSAHS), in which OSA is associated with daytime sleepiness, has been estimated to be 4% of men and 2% of women. However, more recent studies suggest that this may be an underestimation of the prevalence given the increasing age of the general population and increasing prevalence of obesity. Although it has not been extensively studied, the prevalence of OSA in intensive care unit (ICU) patients is likely even higher than in the general population since patients with OSA frequently have comorbid conditions that are common in patients admitted to the ICU, such as obesity, diabetes mellitus, hypertension, ischemic heart disease, heart failure, and

cerebrovascular disease. Recognizing and treating OSA is important because in certain hospitalized patients, such as those in the postoperative period, OSA has been associated with a significant increase in the risk of respiratory failure, cardiac events, and transfer to the ICU.

CSA can occur in the setting of severe heart failure (Cheyne-Stokes respirations [CSR]), stroke, or narcotic use. CSR are characterized by central apneas followed by crescendo-decrescendo periods of hyperventilation. It occurs in approximately 40% of patients with congestive heart failure (CHF) and is even more prevalent in inpatients with decompensated CHF. The cause of this breathing pattern in CHF is increased chemosensitivity to changes in partial pressure of carbon dioxide (P_{CO_2}) levels, as well as the circulatory delay between the lung and carotid chemoreceptors. Treatment of the underlying heart failure is important, but positive airway pressure, whether via noninvasive ventilation or invasive mechanical ventilation, has the potential to improve CSR.

Obesity hypoventilation syndrome (OHS) describes hypoventilation during sleep occurring in patients who are obese, which results in daytime hypercapnia. The diagnostic criteria for OHS are outlined in Table 14.3. The prevalence of OHS in the general population is not well defined, but based on the prevalence of severe obesity and the association of OHS with OSA, the prevalence of OHS has been estimated at 0.6%. There are data to suggest that in patients hospitalized with hypercapnia, the likelihood of OHS as the cause for hypercapnia increases significantly with increasing body mass index (BMI). Hypercapnia can occur in the setting of severe OSA alone, obesity-induced sleep-related hypoventilation without apneic or hypopneic events, or often in combination.

TABLE 14.3 Diagnostic Criteria for Obesity Hypoventilation Syndrome

BMI > 30 kg/m^2

Arterial P_{CO_2} > 45 mm Hg
Other causes of hypoventilation are ruled out.
With or without concomitant OSA

BMI, body mass index; OSA, obstructive sleep apnea; P_{CO_2}, partial pressure of carbon dioxide.

OSA and obesity hypoventilation should be considered in patients with hypercapnic respiratory failure who have any of the signs and symptoms listed in Table 14.4. Moreover, both OHS and OSA are associated with pulmonary hypertension, but patients with isolated OSA tend to have milder pulmonary hypertension. CSA should also be considered if there is a history of CHF, stroke, or opioid use. In patients with hypercapnia related to OSA alone, continuous positive airway pressure (CPAP), at a pressure that resolves the obstructive events, should correct the hypercapnia. However, in patients in whom there is a component of ongoing sleep-related hypoventilation, bilevel positive airway pressure (BiPAP) is usually required. The expiratory positive airway pressure (EPAP) setting is used to maintain airway patency, while the inspiratory positive airway pressure (IPAP) setting is used to ventilate the patient. The larger the difference between the IPAP and EPAP, the larger the tidal volume that is delivered. There is also the mode of volume-assured pressure support (VAPS) in which an EPAP is set, as well as an IPAP minimum, IPAP maximum, backup respiratory rate, and either tidal volume or alveolar ventilation is targeted as the ventilatory goal. During inspiration, the machine will start at the minimum IPAP, but if the ventilatory goal is not met, the machine will automatically adjust the IPAP, up to the maximum IPAP if needed, to meet the goal. VAPS provides reassurance that a similar tidal volume or alveolar ventilation will be maintained between breaths even if there are changes in airway resistance or pulmonary compliance.

TABLE 14.4 **Signs and Symptoms of Obstructive Sleep Apnea-Hypopnea Syndrome and Obesity Hypoventilation Syndrome**

Obesity
Snoring
Awakening snorting or gasping
Witnessed apneas
Excessive daytime somnolence
Morning headaches
Large neck circumference (>16 inches for women, >17 inches for men)
Unrefreshing sleep
Poorly controlled hypertension
Craniofacial abnormalities (micrognathia, retrognathia, macroglossia)
Nocturnal oxygen desaturations
Hypercapnia not explained by other etiology

Treatment of CSA typically requires BiPAP with a set backup respiratory rate. Although CPAP or BiPAP may be effective in treating some patients with combined OSA and CSA, there is an additional mode (adaptive servo-ventilation [ASV]) that is effective at treating patients with both types of apnea. ASV provides an adjustable EPAP, adjustable inspiratory pressure support, and an auto backup rate. However, a landmark study demonstrated increased cardiovascular mortality in patients with heart failure with a reduced ejection fraction who were treated with ASV compared to controls. The American Academy of Sleep Medicine therefore recommends that ASV not be prescribed to these patients if their ejection fraction is less than or equal to 45%.

Unfortunately, there is not much guidance in the literature for empirically picking pressures for CPAP or BiPAP in the setting of

sleep-disordered breathing and sleep-related hypoventilation. In the outpatient setting, a split-night sleep study is performed, in which the first part of the study allows for the diagnosis of sleep-disordered breathing, and the second part of the study allows for titration of CPAP or BiPAP. In patients with no significant comorbidities and evidence of OSA alone, an autotitrating positive airway pressure (auto-PAP) device, whereby the machine automatically titrates the pressures to overcome obstructive events, may be appropriate. If an inpatient sleep study is available, this would be the best way to establish a diagnosis of OSA, CSA, or OHS, and the optimal way to determine the necessary pressures required to treat the disorder. However, if a patient requires initiation of therapy without the benefit of a sleep study, it should be initiated in a closely monitored setting such as an ICU or step-down unit. Monitoring of the P_{CO_2} levels is important if hypercapnia is the presenting abnormality.

Patients who are morbidly obese or have very severe OSA will frequently require higher pressures to resolve the sleep-disordered breathing. If the empiric pressure is too low, then the apnea events or hypoventilation may not be fully resolved, leading to prolonged hypoxemia. Severe hypoxemia has been reported to occur during the empiric use of CPAP. If the empiric pressure is too high, then the patient may experience other complications related to positive pressure, as outlined in Table 14.5, which may decrease the patient's ability to comply with CPAP or BiPAP. These complications include treatment-emergent central apneas in which patients who previously had predominantly obstructive events develop central respiratory events while on positive airway pressure.

TABLE 14.5 Potential Complications and Side Effects of Continuous Positive Airway Pressure or Bilevel Positive Airway Pressure

Nasal/oral dryness
Eye dryness
Mask leak

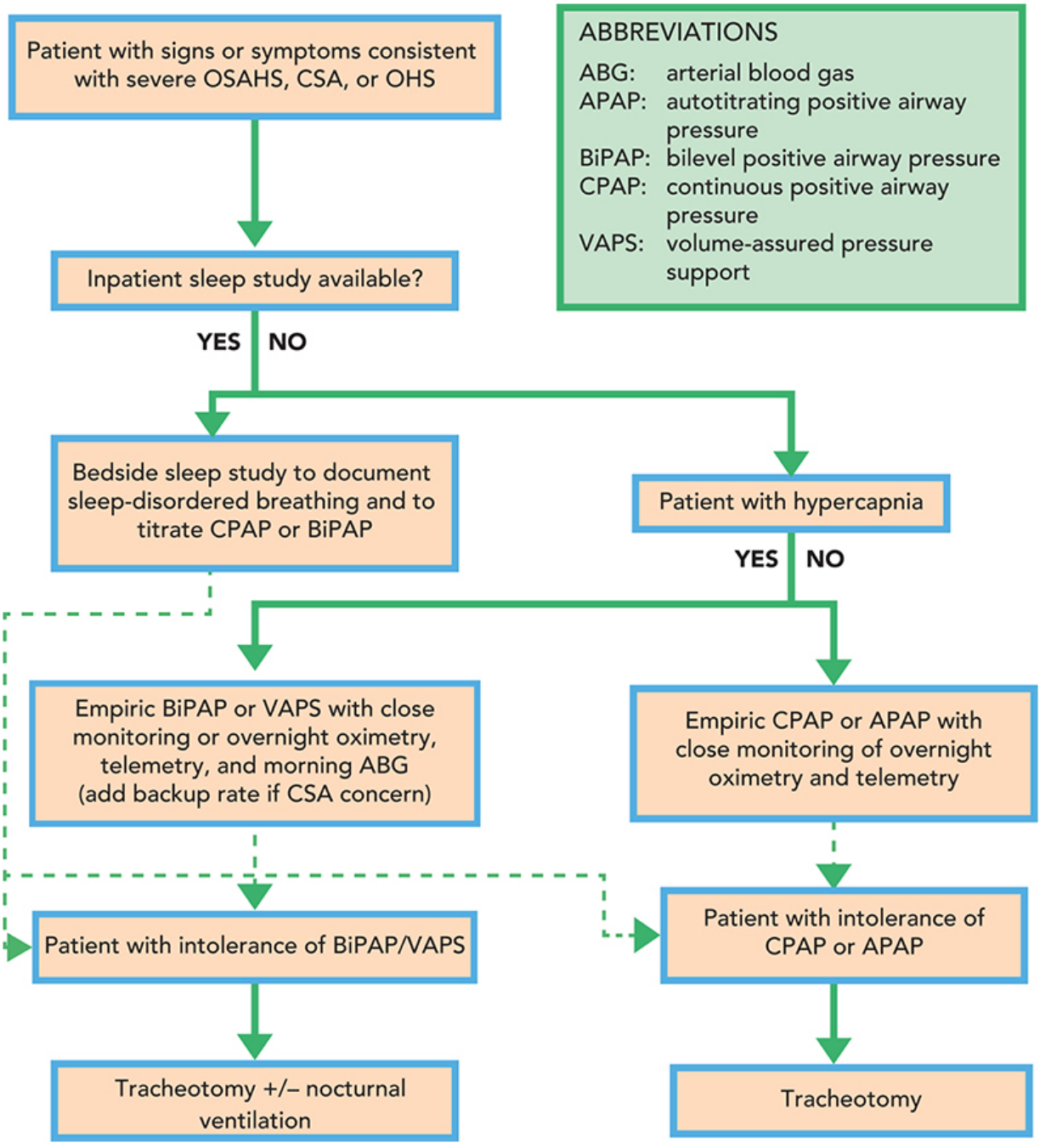
Aerophagia/gastric distension
Skin irritation
Rhinitis/rhinorrhea
Treatment-emergent central apneas
Intolerance of pressure

Based on a recent study, for patients who are unable to tolerate PAP therapy, hypoglossal nerve stimulation appears to improve apnea-hypopnea index (AHI), as well as reduce daytime sleepiness and improve quality-of-life measures. The hypoglossal nerve stimulator is a pacemaker-like device that triggers the hypoglossal nerve to protrude the tongue forward in order to relieve obstructive events. The impulse generator for the device is typically implanted in the right mid-infraclavicular region and can be seen on chest x-ray. The stimulation lead is implanted in the neck, and the sensing lead is implanted in the intercostal muscles on the right lower chest. The patient uses a wand to turn the impulse generator on and off. Of note, depending on the generation of the implanted stimulator, these devices may or may not be MRI compatible. It is important to reach out to the manufacturer to ensure that the device is compatible with any planned imaging.

In patients who cannot tolerate CPAP or BiPAP, tracheotomy is the gold standard for the treatment of OSA because it allows for the upper airway obstruction to be bypassed. However, some patients who are morbidly obese may require custom tracheotomy tubes in order to fully resolve the obstruction. In addition, if there is a component of CSA or sleep-related hypoventilation not solely due to OSA, then nocturnal ventilation through the tracheotomy tube is required. Algorithm 14.1 provides a proposed algorithm for the evaluation and treatment of patients in the ICU who are suspected of having severe OSA or sleep-related hypoventilation.

ALGORITHM 14.1 **Proposed Evaluation and Treatment Guideline for Intensive Care Unit Patients Suspected of Having Severe Obstructive**

Sleep Apnea-Hypopnea Syndrome (OSAHS), Central Sleep Apnea (CSA), or Obesity Hypoventilation Syndrome (OHS)


Patient with signs or symptoms consistent with severe OSAHS, CSA, or OHS
ABBREVIATIONS
ABG: arterial blood gas
APAP: autotitrating positive airway pressure
BiPAP: bilevel positive airway pressure
CPAP: continuous positive airway pressure
VAPS: volume-assured pressure support
Inpatient sleep study available?
YES
NO
Bedside sleep study to document sleep-disordered breathing and to titrate CPAP or BiPAP
Patient with hypercapnia
YES
NO
Empiric BiPAP or VAPS with close monitoring or overnight oximetry, telemetry, and morning ABG (add backup rate if CSA concern)
Empiric CPAP or APAP with close monitoring of overnight oximetry and telemetry
Patient with intolerance of BiPAP/VAPS
Patient with intolerance of CPAP or APAP
Tracheotomy +/– nocturnal ventilation
Tracheotomy

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15 Pulmonary Hypertension and Right Ventricular Failure in the Intensive Care Unit

Maanasi Samant and Murali M. Chakinala

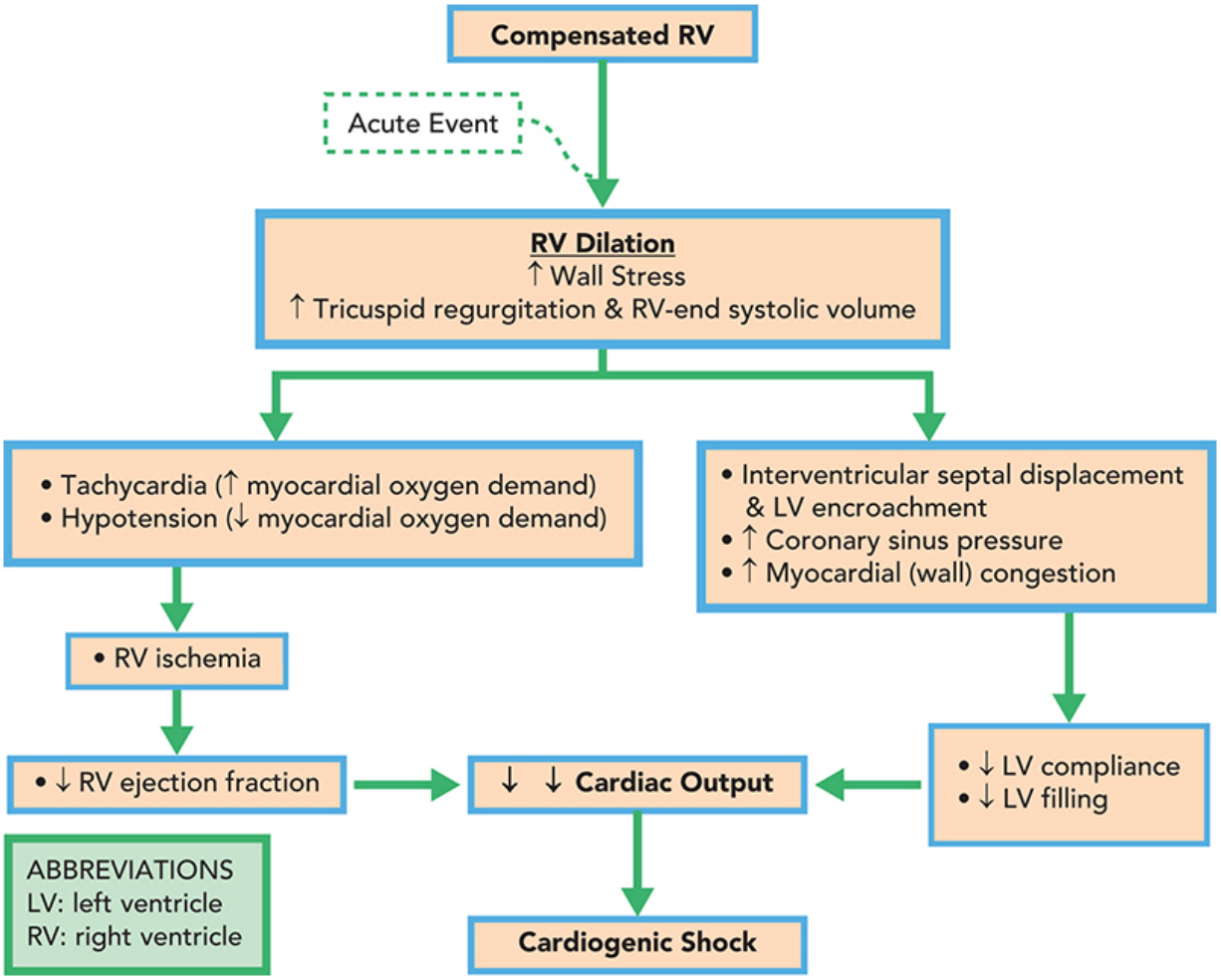
Decompensated right ventricular failure (DRVF) is a less common cause of shock, which is frequently underdiagnosed, and its recognition requires vigilance for a constellation of symptoms and signs. Treatment of DRVF also differs somewhat from routine shock management as elucidated elsewhere in this book. Most often, DRVF occurs in the setting of chronic pulmonary hypertension (PH) (ie, mean pulmonary artery [PA] pressure ≥20 mm Hg) with an inciting acute illness that converts a compensated right ventricle (RV) into DRVF and a hemodynamically unstable situation.

Pathophysiology of Right Ventricle Failure

The RV is a thin-walled chamber that empties by sequential contraction into a low-resistance, high-capacitance pulmonary vascular circuit over the entire period of RV systole. Under normal conditions, a 3- to 4-fold increase in cardiac output should not significantly increase pulmonary pressures and RV workload, thanks to vasodilation and recruitment of the pulmonary vasculature. However, when faced with an acute rise in afterload (eg, massive pulmonary embolism), the RV can decompensate rapidly, leading to shock (Algorithm 15.1). In the setting of chronic PH, the RV has an innate but limited ability to undergo myocardial hypertrophy, reduce wall tension, and maintain contractility. With time, contractility can decrease in the face of increasing afterload, leading to RV dilation. In DRVF, reduced preload to the left ventricular (LV) and intraventricular

septal displacement impairs LV filling, further reducing cardiac output (Algorithm 15.1).

ALGORITHM 15.1 **Pathophysiology of Decompensated Right Ventricular Failure**



Causes of Decompensated Right Ventricular Failure

Table 15.1 lists the causes of acute RV failure. Table 15.2 lists the etiology of acute-on-chronic decompensation in patients with known PH.

TABLE 15.1 Etiology of Right Ventricular (RV) Failure

Left ventricular dysfunction
RV infarct or perioperative injury
Cardiac tamponade (mimicker of RV failure)
Tricuspid valve disease (regurgitation, stenosis)
Acute massive pulmonary embolus (thrombus, fat, air, or amniotic fluid)
Acute lung injury/adult respiratory distress syndrome
Sickle cell chest syndrome
Congenital heart disease (eg, atrial septal defect, anomalous pulmonary venous return, Ebstein anomaly)
Acute decompensation of chronic pulmonary arterial hypertension (Table 15.2)

Diagnosis of Decompensated Right Ventricular Failure

CLINICAL PRESENTATION

DRVF typically manifests as a shock due to a low flow state. A history of PH raises the possibility for an acute-on-chronic decompensation due to any of the causes listed in Table 15.2. Signs and symptoms of DRVF are shown in Table 15.3. Classic presentation is peripheral findings of heart failure in the absence of pulmonary edema.

TABLE 15.2 Causes of Acute Hemodynamic Instability in Chronic Pulmonary Arterial Hypertension

Acute medication failure (eg, noncompliance, interruption of parenteral vasodilator therapy)
Dietary or fluid indiscretion
Increased metabolic demands (eg, infection, fever, environmental heat, pregnancy)
Venous thromboembolism (submassive or massive)
Induction of general anesthesia
Surgery (left-sided valvular repair, pulmonary thromboendarterectomy, lung transplantation, lobectomy, or pneumonectomy)

Dysrhythmias Endocrinopathies (eg, thyroid disorders, adrenal insufficiency)

TABLE 15.3 Signs and Symptoms of Decompensated Right Ventricular Failure

Symptoms	Signs
Syncope, dizziness	Decreased pulses
RUQ pain	Cool extremities
Abdominal distension	Lower extremity edema
Weight gain Lower extremity edema	Elevated jugular venous pulsation (without auscultatory crackles)
Early satiety	Right-sided S3
Dyspnea	Pulsatile liver Hepatojugular reflux
	Ascites

RUQ, right upper quadrant.

DIAGNOSTIC TESTING

Radiology

Plain radiographs may show enlarged central pulmonary arteries with peripheral pruning if chronic PH is present. Chronic RV enlargement manifests with filling of the retrosternal air space on a lateral chest x-ray. Right-sided pleural effusions rarely may be present but pleural effusions typically indicate LV dysfunction. If an acute pulmonary embolism is suspected, lower extremity Doppler examinations and either a VQ scan or pulmonary embolism protocol computed tomography should be obtained.

Electrocardiogram

Table 15.4 shows the RV changes that can be seen by electrocardiography.

TABLE 15.4 Electrocardiographic Changes in Right Ventricular (RV) Failure

Sinus tachycardia
Atrial dysrhythmias (eg, fibrillation, flutter, reentry tachycardia)
Right axis deviation
Right atrial enlargement
Right ventricular hypertrophy
Right bundle branch block
QR pattern in lead V1
S1 Q3 T3 pattern (RV strain)

Laboratory Data

In keeping with a low-output state, typical laboratory values of tissue/organ hypoperfusion may be encountered, including anion gap metabolic acidosis, low central venous or mixed venous oxygen saturation, elevated lactate, (prerenal) blood urea nitrogen to creatinine ratio, and low urine sodium. Hepatic congestion results in elevated liver enzymes and hyperbilirubinemia. RV strain can result in significantly elevated B-type natriuretic peptide, while an elevated troponin I level indicates RV ischemia.

Echocardiography

Cardiac echocardiography is arguably the most useful examination in this scenario by establishing RV failure and excluding significant left-sided pathology. Table 15.5 lists echocardiographic findings in DRVF. It provides rapid and important data for diagnosing RV failure, elucidating precipitating causes and triaging patients into three groups: RV failure with elevated PA pressures, RV failure without elevated pressures, and pericardial disease (Algorithm 15.2).

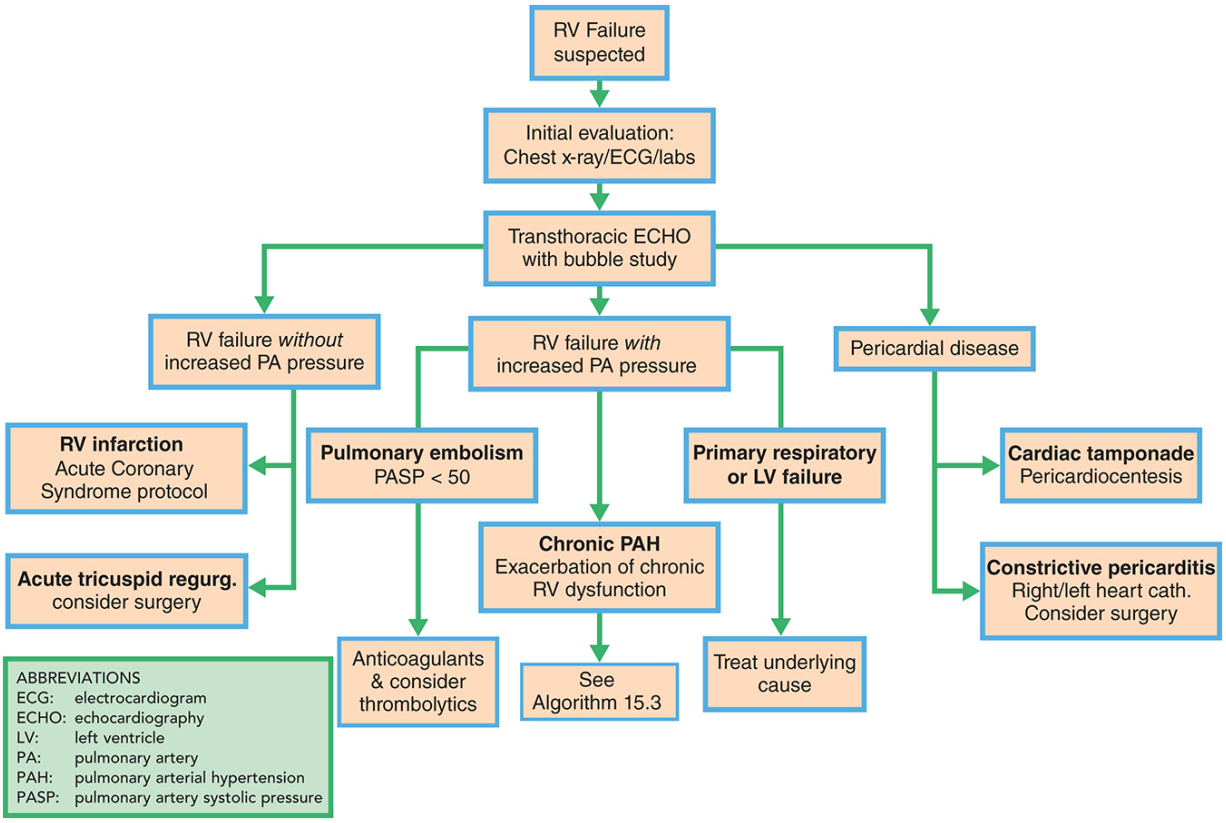
TABLE 15.5 Echocardiographic Findings in Right Ventricular (RV) Failure

RV hypertrophy (in chronic pulmonary hypertension)
RV dilation and hypokinesis
- *McConnell sign*—akinesis of mid-RV free wall with preserved apical wall function is a specific (~95%) sign of acute pulmonary embolism.
- *60/60 sign*—discordancy between mean PAP (estimated by RV outflow tract acceleration time) and PASP (estimated by tricuspid regurgitation jet)

Paradoxical septal motion due to RV pressure overload
Right atrial enlargement
Hyperdynamic left ventricle due to underfilling (ventricular interdependence)
D-shaped left ventricle and late diastolic left ventricular filling
Pericardial effusion
Tricuspid regurgitation
Elevated pulmonary arterial systolic pressure
Pulmonary artery dilatation
Dilated inferior vena cava or lack of inspiratory collapse
Markers of RV function:
Reduced tricuspid annular plane systolic excursion (TAPSE: normal ≥ 2.0 cm)
Reduced tricuspid valve annulus systolic velocity (s') on tissue doppler (normal ≥ 10 m/s))
Reduced RV free wall strain (<−20%)

PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; TV S', tricuspid annular systolic velocity.

ALGORITHM 15.2 Diagnostic Pathway in Suspected Right Ventricular (RV) Failure


RV Failure suspected
Initial evaluation: Chest x-ray/ECG/labs
Transthoracic ECHO with bubble study
RV failure *without* increased PA pressure
RV failure *with* increased PA pressure
Pericardial disease
RV infarction Acute Coronary Syndrome protocol
Pulmonary embolism PASP < 50
Primary respiratory or LV failure
Cardiac tamponade Pericardiocentesis
Acute tricuspid regurg. consider surgery
Chronic PAH Exacerbation of chronic RV dysfunction
Constrictive pericarditis Right/left heart cath. Consider surgery
Anticoagulants & consider thrombolytics
See Algorithm 15.3
Treat underlying cause
ABBREVIATIONS
ECG: electrocardiogram
ECHO: echocardiography
LV: left ventricle
PA: pulmonary artery
PAH: pulmonary arterial hypertension
PASP: pulmonary artery systolic pressure

Pulmonary Artery Catheter

A complementary diagnostic tool in the management of DRVF is the pulmonary artery catheter (PAC). Indications for the use of a PAC include differentiating “pump failure” from other causes of shock or assisting with the management of DRVF (ie, optimizing volume status, use of inotropes, and assessing response to pulmonary vasodilators). Challenges to using PAC in DRVF include difficulty introducing the catheter, increased risk of PA rupture from “overwedging” the distal balloon tip, and poor tolerance of arrhythmias. The characteristic pattern of DRVF includes elevated central venous, RV, and PA pressures with reduced cardiac output, stroke volume, and mixed venous oxygen saturation. With end-stage RV failure (or in the setting of RV infarction), PA pressures may decline, as the RV is unable to generate enough force to eject blood into the pulmonary vasculature. The PA wedge pressure is typically low but may be elevated as LV compliance worsens. Cardiac output should be measured by the Fick method as tricuspid regurgitation or

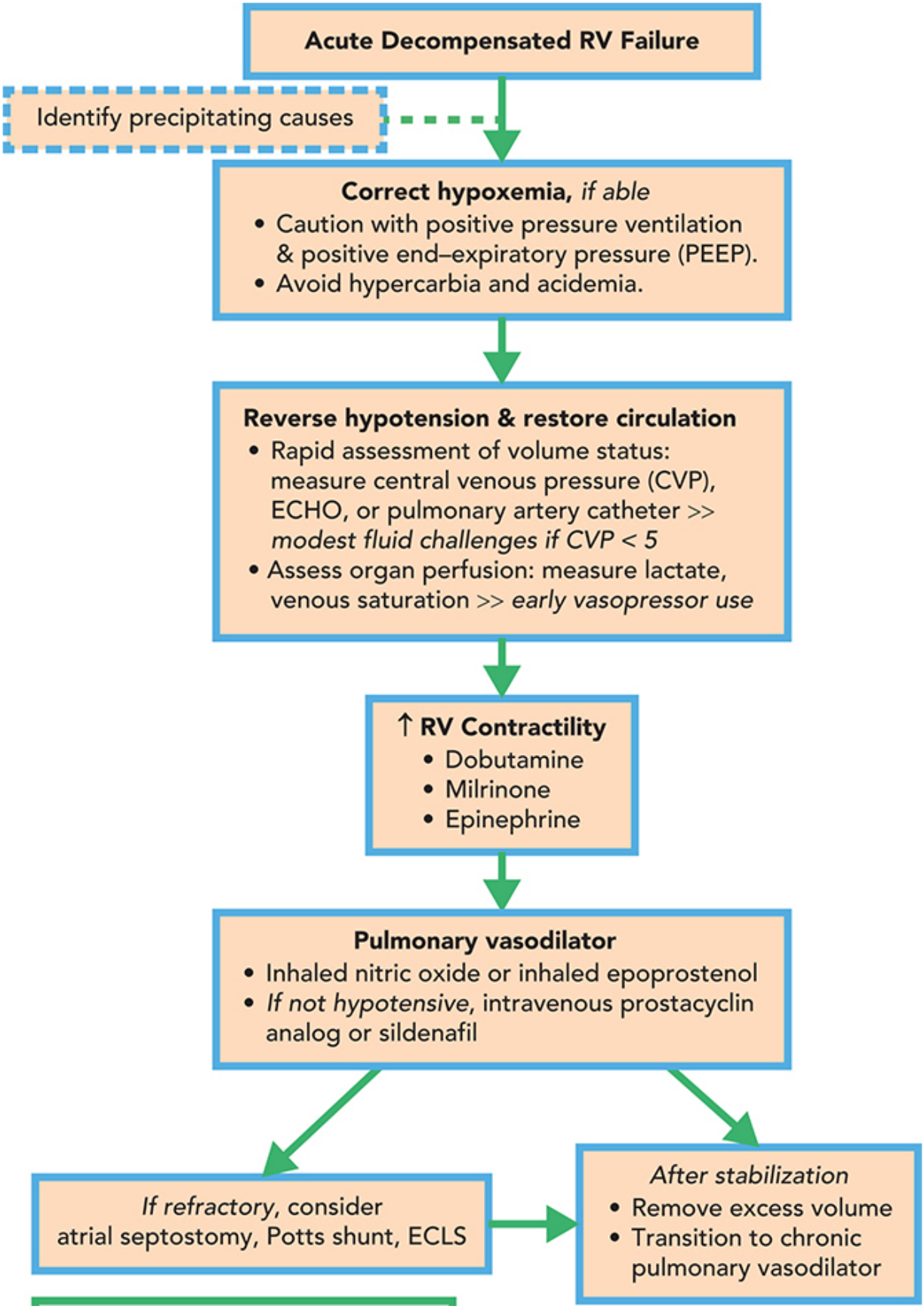
intracardiac shunts make the thermodilution method unreliable. One should place more emphasis on trends gleaned from PAC readings rather than onetime absolute values. Lack of skill in the evaluation of waveforms can lead to poor interpretation of collected data and inappropriate management decisions. Use of PA catheters in managing patients who are critically ill has not shown an improvement in mortality. Their use in DRVF failure with established PH has not been proven to be beneficial. Risks and benefits need to be weighed carefully, and the procedure should be performed and interpreted by skilled individuals.

Treatment of Acute Decompensated Right Ventricle Failure

Treatment of acute DRVF (Algorithm 15.3) includes the following:

- Identify and correct precipitating factors.
- Correct hypoxemia (maybe uncorrectable if right-to-left intracardiac shunt exists).
- Reverse hypotension and restore circulation.
- Treat volume overload and RV encroachment.

ALGORITHM 15.3 **Management of Decompensated Right Ventricular (RV) Failure**


Acute Decompensated RV Failure
Identify precipitating causes
Correct hypoxemia, if able
• Caution with positive pressure ventilation & positive end–expiratory pressure (PEEP).
• Avoid hypercarbia and acidemia.
Reverse hypotension & restore circulation
• Rapid assessment of volume status: measure central venous pressure (CVP), ECHO, or pulmonary artery catheter >> modest fluid challenges if CVP < 5
• Assess organ perfusion: measure lactate, venous saturation >> early vasopressor use
↑ RV Contractility
• Dobutamine
• Milrinone
• Epinephrine
Pulmonary vasodilator
• Inhaled nitric oxide or inhaled epoprostenol
• If not hypotensive, intravenous prostacyclin analog or sildenafil
If refractory, consider atrial septostomy, Potts shunt, ECLS
After stabilization
• Remove excess volume
• Transition to chronic pulmonary vasodilator

ABBREVIATIONS
ECHO: echocardiography
ECLS: extracorporeal life support

IDENTIFY AND CORRECT PRECIPITATING FACTORS

In patients with known PH and chronic RV dysfunction, precipitating factors (Table 15.2) must be identified and corrected. Maintain a high index of suspicion for occult infection in patients with chronic indwelling venous catheters; empiric therapy to treat bacteremia is appropriate. Sepsis will be poorly tolerated, and fluid resuscitation has to be tempered to avoid aggravating RV dilation and LV encroachment. Atrial tachyarrhythmias should be slowed with digoxin, amiodarone, or cardioversion. Nodal blockers with negative inotropic effects or systemic vasodilatory effects (eg, verapamil, diltiazem) should not be used. Bradycardias may require temporary pacing as the situation demands.

CORRECT HYPOXEMIA

Oxygen is a potent pulmonary vasodilator, and liberal oxygen administration, including high-flow oxygen systems, corrects alveolar hypoxia and minimizes hypoxic vasoconstriction. If positive pressure ventilation is needed, employ the lowest plateau pressures, through low tidal volumes and positive end–expiratory pressures, in order to minimize RV afterload (from intra-alveolar vessel compression) and decreases in venous return, while still maintaining adequate oxygenation and avoiding respiratory acidosis. Hypotension and poor ventilation during intubation can have profound hemodynamic consequences. Ketamine or etomidate should be considered as induction agents, and propofol should be avoided to decrease the risk of hypotension. Vasopressors should be immediately available and in some instances initiated prior to induction or uptitrated prior to administration of induction medications if the patient is already hypotensive. Once intubated, permissive hypercapnia should be avoided as hypoxic pulmonary vasoconstriction is augmented by

hypercarbia. Bronchospasm and agitation are frequently overlooked causes of elevated pulmonary vascular resistance (PVR) in ventilated patients and should be managed aggressively.

REVERSE HYPOTENSION AND RESTORE CIRCULATION

Factors governing RV stroke volume are the same as those for the LV: preload, afterload, and myocardial contractility. Treatment of DRVF encompasses all three parameters.

Preload

Insufficient preload is generally not an issue in DRVF. If shock is due to decreased preload (ie, central venous pressure <5 mm Hg), cautious volume challenges of crystalloid should be employed until central venous pressure is 10 to 12 mm Hg and serial cardiac output assessments should be monitored. Overexuberant volume administration can worsen RV distension and encroach on the LV, further reducing cardiac output and worsening hypotension.

Systemic Hypotension

A low systemic diastolic pressure coupled with elevated RV end-diastolic pressure (common in DRVF) narrows the myocardial perfusion gradient, leading to RV ischemia. Thus, vasopressors have an important role in restoring systemic blood pressure to maintain organ perfusion and minimize RV ischemia. While no agent is superior, norepinephrine has both inotropic and peripheral vasopressor properties without major pulmonary vascular constriction. Vasopressin is a potent peripheral vasoconstrictor with minimal effects on the pulmonary vasculature. The lowest doses of pressors should be used to minimize tachycardia, dysrhythmias, myocardial oxygen consumption, and pulmonary vasoconstriction.

Contractility

Patients with persistently unmet peripheral metabolic needs (eg, elevated lactate) can benefit from inotropic support; options include

dobutamine (2-5 mcg/kg/min), epinephrine (0.05-2.0 mcg/kg/min), or milrinone (0.125-0.5 mcg/kg/min), which requires dosage reduction in renal insufficiency.

Afterload Reduction

Selective pulmonary arterial dilation is a critical therapeutic step in breaking the spiral of RV decompensation. Inhaled agents preferentially lower PVR with minimal decreases in systemic vascular resistance and also minimize ventilation-perfusion mismatching and hypoxemia. Two available agents are inhaled nitric oxide and inhaled epoprostenol. Inhaled nitric oxide up to 40 ppm is administered via face mask or endotracheal tube, but methemoglobin levels must be followed. Inhaled epoprostenol (5,000-20,000 ng/mL) can be delivered as a continuous nebulization. Once cardiac output and blood pressure improve, patients can be transitioned to more conventional and longer-term options (eg, parenteral or longer-acting inhaled prostacyclin analogues). Nonselective vasodilators such as nitroprusside, nitrates, hydralazine, and calcium channel antagonists must be avoided, as they preferentially cause peripheral vasodilation and aggravate hypotension.

TREAT VOLUME OVERLOAD AND RIGHT VENTRICLE ENCROACHMENT

Once circulation is restored and the patient has stabilized, excess volume can be removed. Severe right heart failure can be associated with diuretic resistance, due to poor intestinal absorption, decreased glomerular filtration rate with poor renal arterial perfusion, renal venous congestion from elevated central venous pressures, and intense neurohormonal activation. A suggested stepwise approach is:

1. Loop diuretic (eg, furosemide, bumetanide) by intravenous bolus or continuous infusion. The latter maintains a continuous renal threshold of the drug with constant diuresis and less ototoxicity.

2. If loop diuretic is insufficient, a thiazide diuretic (eg, chlorothiazide [IV or po] or metolazone [po]) can be added; monitor electrolytes closely.
3. Spironolactone is effective in countering the intense neurohormonal pathway and can be added unless hyperkalemia is present.
4. Finally, mechanical fluid removal with slow continuous venovenous ultrafiltration may be appropriate.

Mechanical Support

Patients refractory to optimal pharmacologic therapies could be considered for extracorporeal life support (ECLS). Mechanical support is increasingly considered as an option to bridge to definitive treatment, such as advanced chronic pulmonary vasodilator therapy (eg, epoprostenol), lung transplantation, or pulmonary thromboendarterectomy in the setting of chronic thromboembolic disease. Prior to the initiation of such measures, it is most important to address the patient's bridging potential as well as their underlying LV function. Some of the contraindications to initiating ECLS include major contraindications for anticoagulation, irreversible end-organ damage, and irreversible cardiopulmonary failure in a patient that is not a transplant candidate. There are several modes of mechanical support for RV failure, but venoarterial (VA) extracorporeal membrane oxygenation (ECMO) is typically required. The evidence for using VA ECMO in isolated right ventricular failure comes predominantly from case reports or case series. Assist devices (eg, Impella, right ventricular assist device) can be surgically or percutaneously implanted but have not been used in severe pulmonary arterial hypertension (PAH) due to the risk of pulmonary hemorrhage. The hemodynamic effects of these devices depend on whether there is isolated right ventricular failure or biventricular failure. The decision to initiate mechanical support should be made

by a multidisciplinary team comprised of an intensivist, pulmonologist/cardiologist, and cardiothoracic surgeon.

Surgical Interventions

Atrial septostomy, which is the percutaneous creation of a right-to-left shunt in the interatrial septum, allows for right-sided decompression and improved left-sided filling. Although right-to-left shunting results in oxygen desaturation, this is counterbalanced by improved cardiac output and total oxygen delivery. Surgically or percutaneously created Potts shunt, which is an anastomosis between the left PA and the descending aorta, offers an alternative palliation strategy. Septostomy and Potts shunts are risky procedures with associated morbidity and mortality that should only be performed at experienced centers.

General Measures

1. Control agitation.
2. Suppress fevers.
3. Place filters on intravenous catheters to prevent air embolization if intracardiac shunt present.
4. Deep venous thrombosis prophylaxis
5. Minimize Valsalva maneuvers (eg, constipation).
6. Caution with colloid infusions, but consider transfusion if anemic and if oxygen delivery is severely compromised.

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16 Pulmonary Embolism

Roger D. Yusen

A significant proportion of patients with pulmonary embolism (PE) receive care in the intensive care unit (ICU). Some are transferred to the ICU because of PE, while others develop PE during their ICU stay. For some ICU patients with suspected PE, their clinical conditions may preclude them from being transported out of the ICU for testing. For patients diagnosed with PE, factors such as the severity of PE and the risks of death, hemodynamic deterioration, and bleeding help in guiding treatment decisions.

Pathophysiology

Acute PE decreases perfusion to the affected areas of the lung. In areas with adequate ventilation, PE results in alveolar dead space, wasted ventilation, and decreased alveolar-capillary gas exchange. Consequently there is a significant reduction in alveolar CO_2 content, resulting in lower levels of exhaled CO_2, end-tidal CO_2 ($Etco_2$), and the fraction of $Etco_2/Paco_2$. Redistribution of blood flow away from areas affected by PE causes overperfusion of other lung regions and their transformation into low ventilation/perfusion ($\dot{V}/\dot{Q}$) regions. This significant $\dot{V}/\dot{Q}$ mismatch causes hypoxemia and an increased alveolar-to-arterial oxygen gradient ($PA\text{-}ao_2$). Hypoxemia, anxiety, and pain (eg, from infarction and pleural inflammation) may lead to stimulation of the respiratory drive. Some patients with PE hyperventilate and have low $Paco_2$ without hypoxemia, although an elevated $PA\text{-}ao_2$ would demonstrate an abnormal alveolar gas exchange. Patients with underlying conditions (eg, lung disease,

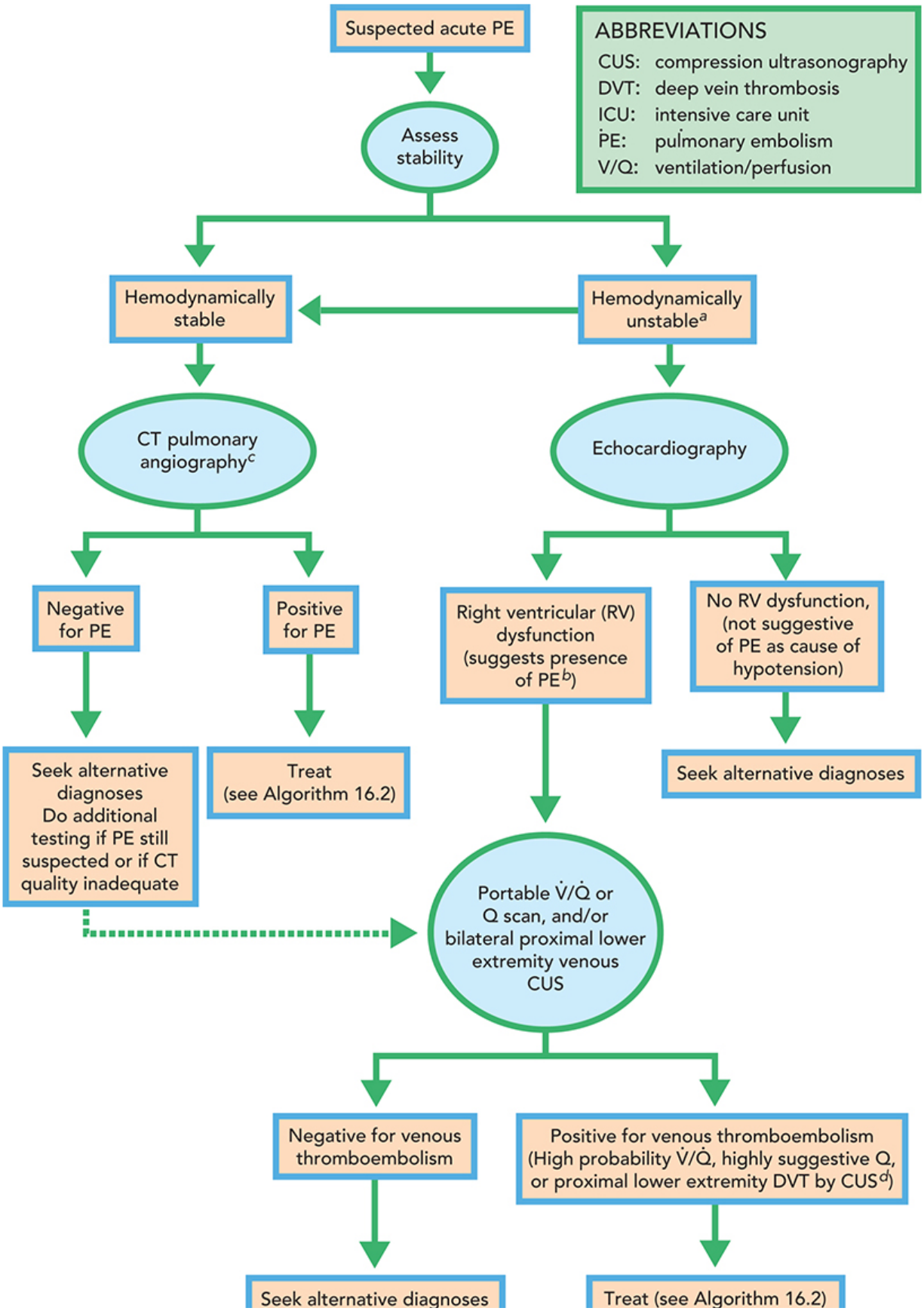
sedation) may not increase ventilation as expected. A small proportion of patients with underlying lung disease may initially hyperventilate but then decompensate, leading to development or worsening of hypercapnic respiratory failure. Acute pulmonary hypertension (PH) resulting from PE could worsen hypoxemia as a result of decreased cardiac output (CO) with low central venous and mixed venous oxygen saturation, or via intracardiac right-to-left shunting through a patent foramen ovale.

Through vasoactive mediators, anatomic obstruction, and hypoxic vasoconstriction, acute PE may cause elevation of pulmonary vascular resistance (PVR) and subsequent right ventricular (RV) dilatation, increased RV pressure and volume, and increased RV wall tension and myocyte stretching. Right heart *dysfunction* has abnormal right heart function test values (eg, RV hypokinesis on echocardiogram). Right heart *failure* has signs and symptoms of systemic congestion resulting from impaired RV filling or reduced RV output due to right heart structural or functional abnormalities. Associated prolongation of RV contraction time into early left ventricular (LV) diastole leads to interventricular septum leftward bowing. Desynchronization of the ventricles and impeded early diastolic LV filling may lead to reduced CO, systemic hypotension, and hemodynamic instability. RV ischemia may result from systemic hypotension, reduced coronary driving pressure, hypoxemia, and increased RV myocyte oxygen demand that exceeds supply. Compensatory mechanisms involving neurohumoral activation, inotropic and chronotropic stimulation, and systemic vasoconstriction may improve blood flow through the obstructed pulmonary vascular bed and stabilize systemic blood pressure (BP). However, acute PE-associated RV failure and the cascade of events described earlier may lead to cardiovascular decompensation and death. Some hemodynamically stable patients with acute PE may subsequently destabilize within 48 hours after the initial PE presentation due to RV decompensation, PE recurrence, or development of myocardial inflammation and cardiac dysfunction.

Diagnosis

PE often has nonspecific *signs and symptoms* (eg, tachycardia, tachypnea, dyspnea, pleuritic chest pain, hemoptysis, presyncope, syncope, hypoxemia, and hypotension), which frequently overlap with other conditions that occur in ICU patients (Algorithm 16.1). The *differential diagnosis* list for patients with signs and symptoms of PE includes sepsis, hypovolemia, acute lung injury (eg, pneumonia, aspiration, transfusion-associated lung injury [TRALI]), heart failure, transfusion-associated circulatory overload (TACO), acute coronary syndrome, cardiac tamponade, decompensated PH, constrictive cardiac disease, valvular heart disease, and aortic dissection. ICU patients often have multiorgan dysfunction, and PE may occur in conjunction with illnesses such as myocardial dysfunction or sepsis. Clinicians frequently underdiagnose PE because it mimics other diseases, and vice versa. Prompt PE diagnosis allows for appropriate treatment, which will reduce mortality and PE recurrence rates.

ALGORITHM 16.1 **Diagnostic Evaluation for Suspected Acute Pulmonary Embolism in the Intensive Care Unit**


Suspected acute PE
Assess stability
ABBREVIATIONS
CUS: compression ultrasonography
DVT: deep vein thrombosis
ICU: intensive care unit
PE: pulmonary embolism
V/Q: ventilation/perfusion
Hemodynamically stable
Hemodynamically unstable[a]
CT pulmonary angiography[c]
Echocardiography
Negative for PE
Positive for PE
Right ventricular (RV) dysfunction (suggests presence of PE[b])
No RV dysfunction, (not suggestive of PE as cause of hypotension)
Seek alternative diagnoses Do additional testing if PE still suspected or if CT quality inadequate
Treat (see Algorithm 16.2)
Seek alternative diagnoses
Portable V̇/Q̇ or Q scan, and/or bilateral proximal lower extremity venous CUS
Negative for venous thromboembolism
Positive for venous thromboembolism (High probability V̇/Q̇, highly suggestive Q, or proximal lower extremity DVT by CUS[d])
Seek alternative diagnoses
Treat (see Algorithm 16.2)

[a]Search for alternative and concomitant diagnoses.

[b]Try to confirm presence of PE with additional testing.

[c]If contraindication to intravenous (IV) contrast exist, consider $\dot{V}/\dot{Q}$ scan, lower extremity venous CUS, or MR angiography.

[c]Proximal lower extremity DVT serves as a surrogate for PE in the appropriate clinical setting.

DIAGNOSTIC MODALITIES

Since many disorders on the PE differential diagnosis list are life-threatening, clinical suspicion of PE should lead to expeditious objective diagnostic testing. Pretest probability influences the diagnostic workup of patients with suspected PE, and its incorporation into the interpretation of diagnostic tests improves their accuracy. However, clinical probability scores for PE diagnosis have limited ability to decrease testing for PE in the ICU because they often produce an intermediate to high pretest probability of PE. Nonspecific diagnostic tests, such as D-dimer assay, have a low accuracy (eg, many false positives) in the ICU setting, and waiting for results may delay necessary additional diagnostic tests or treatments. While chest x-ray (CXR), electrocardiogram (EKG), and arterial blood gas (ABG) tests may prove useful for assisting in determining pretest probability and for evaluating other causes of a patient's illness, they do not confirm or rule out the diagnosis of PE. *Cardiac biomarkers* (eg, troponin) assist with risk stratification, though they have low diagnostic accuracy. *High-sensitivity troponin assays* have an increased ability to detect myocardial injury in comparison to conventional assays.

Contrast-enhanced chest CT (PE-protocol) pulmonary angiography (CTPA) serves as the primary test for evaluating patients for PE. *Acute PE diagnostic criterion* on CTPA consists of a filling defect within the pulmonary arterial vasculature. A PE may fully occlude a vessel (ie, vessel cut-off), or a nonocclusive PE will show a thin stream of contrast adjacent to PE within the vessel. When

viewed in its axial plane, a vessel may show a thin rim of contrast that surrounds the central filling defect from the PE (Polo Mint sign). The accuracy of CT for PE diagnosis decreases with poorer scan quality and for smaller and more peripheral clots. CT provides an assessment of clot burden, and it may detect PE-associated pulmonary infarction. Assessment for signs of RV dysfunction (ie, RV/left ventricle [LV] internal diameter ratio on four-chamber views or three-dimensional RV volume to LV volume ratio elevation [eg, >0.9], flattening or displacement of the interventricular septum toward the LV, and reflux of contrast into the inferior vena cava [IVC] and hepatic veins) assists with PE risk stratification (ie, signs associated with complicated clinical course, including death). CT also assists with the detection of alternative or concomitant diagnoses. Contraindications to PE-protocol CT include contrast allergy, severe renal dysfunction, or the inability to safely transfer patient out of the ICU. Patients with contraindications to CT or inadequate-quality CT (eg, poor opacification of pulmonary arteries) should undergo other diagnostic testing that may include $\dot{V}/\dot{Q}$ scan, bilateral lower extremity venous compression ultrasonography (CUS), or echocardiography (ECHO).

Radionuclide scintigraphy ($\dot{V}/\dot{Q}$ scan) allows for testing in the ICU because of its portability. In the setting of high clinical suspicion, a high probability (of PE) $\dot{V}/\dot{Q}$ scan result rules in PE unless a mimicking diagnosis is suspected (eg, pulmonary artery [PA] sarcoma, fibrosing mediastinitis). Patients with an abnormal CXR will often receive an indeterminate/nondiagnostic $\dot{V}/\dot{Q}$ interpretation, which warrants further testing. Because of the high likelihood of obtaining a nondiagnostic $\dot{V}/\dot{Q}$ result and since chest CT may reveal alternative or additional diagnoses, chest CT should remain the first-choice diagnostic test for evaluating ICU patients with suspected PE.

CUS may diagnose deep vein thrombosis (DVT) at the bedside in the ICU. Proximal lower extremity DVT may serve as a surrogate marker for PE in the appropriate clinical setting.

ECHO, another portable modality, may detect right-sided cardiac thrombus or signs of right heart dysfunction associated with or suggestive of PE. Findings on ECHO may suggest other etiologies (eg, cardiac tamponade, myocardial infarction, heart failure, valvular heart disease) that explain a patient's signs and symptoms, and it may exclude these and other mimics of PE. A hemodynamically unstable patient (ie, hypotensive/requiring vasopressor therapy) with suspected PE should undergo urgent ECHO. Findings on ECHO to suggest PE include RV dilatation and hypokinesis; increase in RV/left ventricle (LV) diameter ratio (eg, >1.0); elevated PA pressure and PA dilation; tricuspid regurgitation; interventricular septal flattening, dyskinesis, paradoxical motion, or shift toward the LV; decreased tricuspid annular plane systolic excursion (TAPSE; <16 mm); McConnell sign (ie, mid-RV free wall hypokinesis with normal or elevated contractility of the RV apex); and the 60/60 sign (coexistence of a truncated RV outflow tract acceleration time [<60 ms] with a PA systolic pressure >30 and <60 mm Hg). ECHO may detect thrombi in the vena cava, right atrium (RA), or RV, including a thrombus-in-transit, and also a right-to-left shunt (eg, patent foramen ovale). In hemodynamically unstable patients, the absence of ECHO signs of right heart dysfunction practically excludes PE as the cause of instability. Increased RV wall thickness or signs of RV pressure overload greater than expected with acute RV dysfunction suggest that the patient had preexisting right heart and/or pulmonary vascular disease.

STABILITY ASSESSMENT

Cardiovascular stability helps to determine the diagnostic workup for suspected PE in an ICU setting (Algorithm 16.1). *Hemodynamically stable* patients should undergo evaluation with PE-protocol contrast-enhanced chest CT if contraindications do not exist. *Hemodynamically unstable patients* should undergo tests based on the likelihood of ruling in or ruling out diagnoses, test availability, and the ability to obtain rapid results. If a patient cannot be transported out of the ICU for diagnostic testing due to unacceptable risk or other

reasons, the patient should undergo bedside testing (eg, ECHO, portable $\dot{V}/\dot{Q}$ or $\dot{Q}$ scan, bilateral lower extremity venous CUS). An unstable patient who has suspected PE should undergo rapid risk stratification to assess for RV dysfunction (ie, ECHO) and RV injury (ie, cardiac troponin). For patients in *cardiac arrest*, immediate bedside ECHO might also assist with decision-making about interventions such as thrombolytic therapy.

Prognosis

Hemodynamic status remains the most important acute prognostic factor for patients who have acute PE. Although normotensive patients with acute PE without evidence of *RV dysfunction* have a short-term mortality rate of ~2%, the mortality rate increases to around 25% in patients with *shock* and up to 65% in those who present with *cardiac arrest*. RV failure causes approximately half of the PE-associated deaths that occur during the first 30 days after diagnosis of PE. The degree of *hemodynamic instability* in patients with acute PE predicts in-hospital mortality. Higher severity of *PE-associated cardiovascular dysfunction* (ie, ranging from the lowest severity of no cardiovascular dysfunction to higher severity categories of RV dysfunction without arterial hypotension, arterial hypotension, cardiogenic shock, and cardiopulmonary arrest) predicts higher mortality.

Elevated cardiac troponin in the setting of PE suggests *RV injury* has occurred, and it portends a poor prognosis even in hemodynamically stable patients. Patients who have *RV dysfunction*, *RV thrombus*, or *right-to-left shunt* through a patent foramen ovale on ECHO or CT have a higher mortality compared to those without these findings.

RISK STRATIFICATION

Prognostic indicators may assist with risk stratification and decision-making regarding escalation of therapy. The European Society of

Cardiology (ESC) PE treatment guidelines recommend use of an early mortality risk-based classification system to drive treatment decisions (Table 16.1). Prior PE classification systems have used massive, submassive, or other terms to describe each patient's PE clinical severity. Radiographic grading may classify PE clot burden. For acute PE, the ESC guideline uses four key risk assessment categories that assess for (1) *hemodynamic instability* (ie, PE-related persistent hypotension, obstructive shock, or cardiac arrest), (2) *imaging-detected* (ECHO or chest CT) signs of RV dysfunction, (3) *elevated clinical risk score* (by Pulmonary Embolism Severity Index [PESI] or simplified PESI [sPESI]), and (4) *elevated cardiac troponin*. Patients with *high-risk PE* have hemodynamic instability. The high-risk group also includes those with highly suspected PE who have hemodynamic instability and imaging-detected signs of RV dysfunction. Patients with *intermediate-risk PE* do not have hemodynamic instability, and this group is stratified into intermediate-high and intermediate-low groups. Patients with *intermediate-high risk PE* have imaging-detected signs of RV dysfunction and an elevated cardiac troponin. Patients with *intermediate-low risk PE* have either RV dysfunction or elevated cardiac troponin, or neither of these findings combined with an elevated clinical risk score. Patients with *low-risk PE* do not have an elevated clinical risk score, imaging-detected signs of RV dysfunction, or an elevated cardiac troponin.

TABLE 16.1 Mortality Risk Classification of Patients With Acute Pulmonary Embolism

	Risk Parameters and Scores			
Early Mortality Risk	**Shock or Hypotension**	**Elevated PESI or sPESI[a]**	**Signs of RV Dysfunction on ECHO or CTPA[b]**	**Elevated Cardiac Troponin**
High	+	NR	+	NR

	Risk Parameters and Scores			
Early Mortality Risk	**Shock or Hypotension**	**Elevated PESI or sPESI[a]**	**Signs of RV Dysfunction on ECHO or CTPA[b]**	**Elevated Cardiac Troponin**
Intermediate	−	NR	+	+
Intermediate high	−	NR	+	−
		NR	−	+
Intermediate low		+	−	−
Low	−	−	NR or −	NR or −

CTPA, computed tomographic pulmonary angiography; ECHO, echocardiogram; LV, left ventricle; NR, not required (no or any result does not change classification); PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricle; sPESI, simplified pulmonary embolism severity index.

[a]sPESI elevated if age >80 years, history of cancer, history of chronic cardiopulmonary disease, pulse ≥110 beats/min, systolic blood pressure <100 mm Hg, or Sao_2 <90%. PESI also includes the variables of male gender, respiratory rate ≥30 breaths/min, temperature <36 °C, and mental status altered, and its scoring uses a point system that differs from sPESI.

[b]Echocardiographic (echo) criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV/LV internal diameter ratio (>1.0), RV free wall hypokinesis, or increased velocity of the tricuspid regurgitation jet. CTPA (four-chamber views of the heart) criterion for RV dysfunction consists of an increased end-diastolic RV/LV internal diameter ratio (>1.0).
Adapted from Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54:1901647 (Table 8).

The ESC guideline does have some limitations. The risk stratification schema does not address many pertinent comorbid conditions. In patients with acute PE, indicators of poor prognosis or adverse outcomes not included in the risk stratification schema include coexisting proximal lower extremity DVT, large thrombus burden, and RV thrombus. The risk stratification schema also does

not include some important clinical events, such as new or worse hypoxemia, respiratory failure requiring mechanical ventilation, or degrees of or worsening of cardiovascular status that might occur within a specific risk class (eg, greater tachycardia, lower BP but not hypotensive).

Other risk stratification/prognostic tools include but are not limited to the *Shock Index* (heart rate [HR]; beats per minute [bpm])/BP [mm Hg]; high risk >1.0), the *Bova score* (systolic BP 90-100 mm Hg [2 points], cardiac troponin elevation [2 points], RV dysfunction [2 points], and HR >110 bpm [1 point]; highest risk > 4 total points), and the *modified FAST score* (age-adjusted elevation of high-sensitivity troponin, syncope, and HR ≥100 bpm; highest risk, all three conditions present). These tools assist with prognostication within the ESC low-risk and intermediate-risk groups.

TRIAGE

Patients with high-risk acute PE should receive ICU care. Patients with intermediate-high risk PE may benefit from ICU monitoring for 1 to 2 days. We recommend ICU care for intermediate-low or low-risk PE patients with severe or significantly worsening respiratory or cardiovascular status.

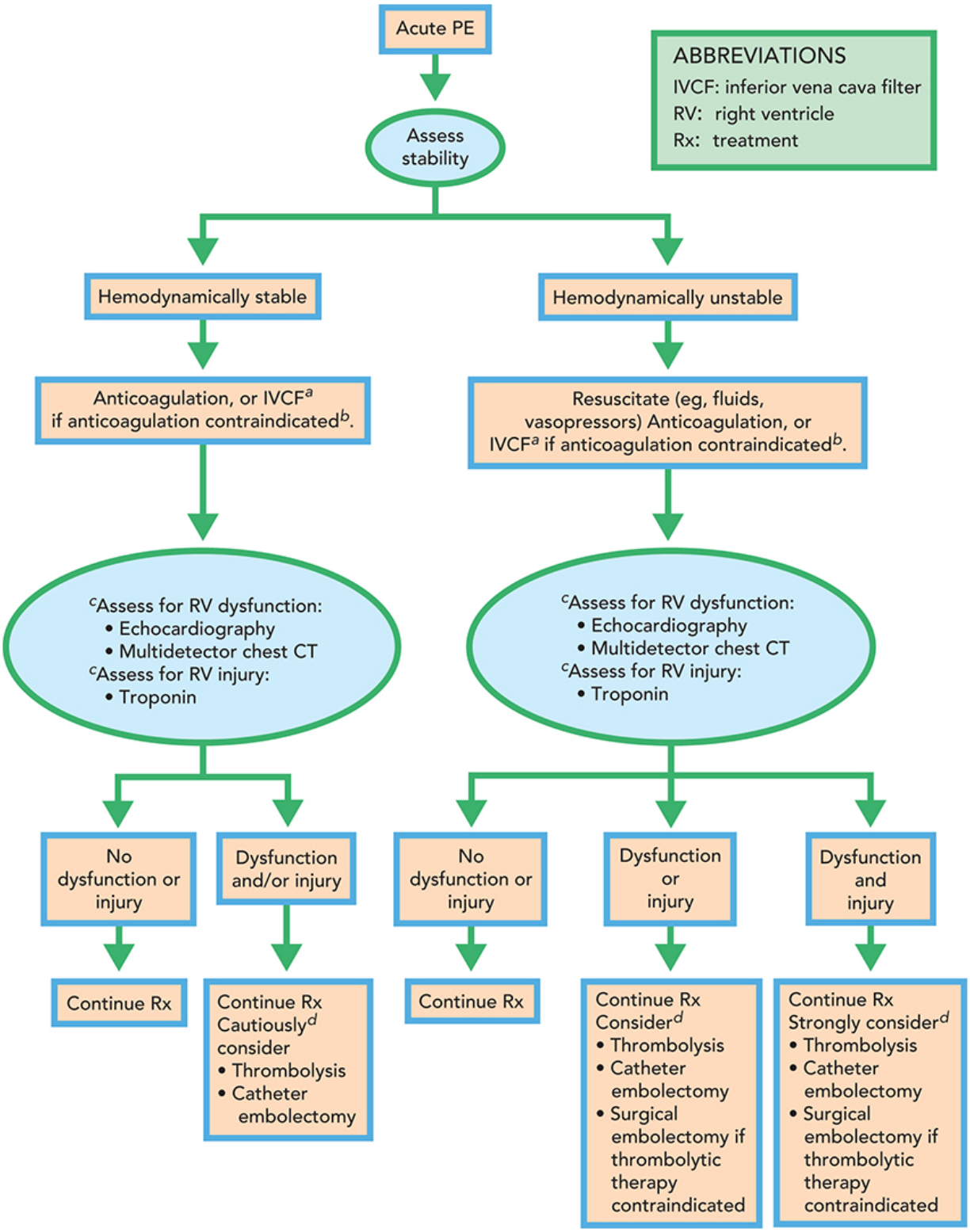
A multidisciplinary expert PE Response Team (PERT) may aid in acute PE management decisions. PERT teams may recommend transferring a patient from a non–ICU bed to the ICU, suggest additional diagnostic and risk stratification testing, provide treatment recommendations, and facilitate the involvement of personnel from pulmonology, cardiology, hematology, interventional radiology, cardiothoracic surgery, and other relevant groups.

Treatment

GENERAL APPROACHES

Clinicians should make their treatment decisions for PE based on their confidence in the diagnosis of PE, hemodynamic status, degree of RV dysfunction/injury, bleeding risk, prognosis, comorbidities, and patient preferences. For patients deemed to have a high clinical probability of PE and an acceptable bleeding risk, clinicians should promptly initiate anticoagulation upon the initial *suspicion* of PE and before confirming or excluding the diagnosis. Satisfactory "exclusion" of the diagnosis of PE should lead to prompt discontinuation of anticoagulation, unless otherwise indicated, and initiation of venous thromboembolism (VTE) prophylaxis. Confirmation of PE should lead to continuation of or prompt initiation of anticoagulation if not contraindicated. Confirmation of PE in the setting of a contraindication to anticoagulation, and possibly the failure of therapeutic doses of anticoagulation, should lead to placement of an IVC filter. Prompt risk stratification will assist with further decisions regarding escalation of PE treatment (ie, thrombolytic therapy, catheter-based therapy, or surgical embolectomy) (Algorithm 16.2).

ALGORITHM 16.2 **Treatment of Acute PE in the Intensive Care Unit**



[a]Temporary or permanent IVCF.

[b]Anticoagulate after IVCF placement once contraindication to anticoagulation resolves.

[c]See Table 16.1.
[d]Assess for contraindications.

Resuscitation for acute hypoxemic respiratory failure should include *supplemental oxygen* and *ventilatory support* as deemed necessary. Patients who are hypotensive from PE have a high risk of hemodynamic collapse during endotracheal intubation and mechanical ventilation. Induction agents used to facilitate intubation may cause a decrease in sympathetic tone and systemic BP, thereby reducing both RV perfusion and RV preload. Induction agents may also have a direct negative inotropic effect on the myocardium, further decreasing CO. Therefore, it is recommended to avoid potent vasodilators/negative inotropes (eg, *propofol*) and instead use the most hemodynamically neutral agents (eg, *etomidate*, *ketamine*). During the intubation procedure, apnea may lead to hypoxemia and hypercapnia and a subsequent acute increase in PVR. Close hemodynamic monitoring with vasopressor agents readily available may reduce the risk of cardiovascular collapse. Positive pressure ventilation, particularly with excessively high tidal volumes, may increase PVR and worsen RV dysfunction. Low tidal volumes and atelectasis may also increase PVR. Hence, we recommend a lung-protective ventilation strategy (tidal volume 6 mL/kg lean body weight and end-inspiratory plateau pressure <30 cm H_2O) similar to that used in acute respiratory distress syndrome (ARDS). Higher positive end-expiratory pressure (PEEP) levels may extrinsically compress pulmonary vasculature and increase PVR, whereas an optimal PEEP level may increase alveolar recruitment, improve oxygenation, reduce hypoxic vasoconstriction, and lower PVR.

The treatment of RV failure includes optimization of RV preload and afterload and augmentation of RV contractility. *Hemodynamically unstable patients* who have PE should undergo stabilization and resuscitation (see Chapter 6) with cautious fluid management, vasopressor treatment, and consideration of inotropic support.

Fluid management should aim to optimize cardiac preload and avoid exacerbating RV pressure overload. A low central venous pressure (CVP) or a nondilated IVC would support judicious

intravascular volume expansion, and an elevated CVP would suggest cautious use of diuretic therapy.

Vasopressor therapy should aim to improve low systemic BP, systemic perfusion, coronary perfusion to the RV, and ratio of systemic vascular resistance (SVR) to PVR. For the failing RV and the associated decreased LV filling, inotropic therapy should aim to augment CO to a level commensurate with organ perfusion. Since *norepinephrine* (eg, 0.025-1.0 mcg/kg/min IV) has alpha-adrenergic and beta-adrenergic properties, which should increase systemic pressure and modestly improve inotropy, we recommended it as the first-line agent for shock secondary to PE. For a norepinephrine dose of more than 15 mg/min IV, consider adding *vasopressin* (0.04 U/min IV). We recommend *epinephrine* (eg, up to 0.01-1.0 mcg/kg/min) as a second-line therapy because of concerns about an increased risk of tachycardia and arrhythmias. After treating hypotension with vasopressor therapy, if CO appears to need further augmentation, then we recommend a trial of *dobutamine* (typically 2-5 mg/kg/min IV, and uncommonly up to 10 mg/kg/min). Monitor metrics of end-organ perfusion such as urine output, mental status, and capillary refill, echocardiographic assessment of RV function and CO, and central venous oxygen saturation of hemoglobin (CVO_2%) to help guide vasopressor and inotrope titration. We recommend a goal CVO_2% of 65% to 70%. With stable Hgb and estimates of oxygen consumption, changes in CVO_2% will reflect changes in CO.

Studies have not strongly supported the use of pulmonary vasodilators, such as *inhaled aerosolized nitric oxide* or *inhaled aerosolized epoprostenol*. We recommend against the use of systemic pulmonary vasodilator therapy because of the risk of exacerbating systemic hypotension and worsening $\dot{V}/\dot{Q}$ mismatch and hypoxemia.

Mechanical circulatory support (ie, extracorporeal membrane oxygenation [ECMO]) may have efficacy in the small proportion of patients who have acute PE-associated circulatory collapse or cardiac arrest, serving as a bridge to escalated therapy. For acute PE-associated circulatory failure, which in most cases predominates

over respiratory failure, *venoarterial (VA)-ECMO* may provide benefits. For acute PE-associated cardiac arrest, particularly when cardiopulmonary resuscitation (CPR) is initiated within 5 minutes of the arrest and return of spontaneous circulation is not achieved within 10 minutes of CPR, consideration should be given to cannulation for and treatment with ECMO during CPR (ECPR). Because of the high bleeding risk, concomitant systemic thrombolytic therapy and ECMO in most cases are avoided.

ANTICOAGULATION

Anticoagulation acts to prevent new clot formation and decrease risk for recurrent VTE. Inhibitory effects on platelet aggregation facilitate clot dissolution and limit release of vasoactive substances. Anticoagulants that have efficacy for the initial treatment of PE include parenteral agents (ie, *unfractionated heparin* [UFH], *low-molecular-weight heparin* [LMWH], eg, enoxaparin and dalteparin), the indirect thrombin inhibitor *fondaparinux*) and oral agents (ie, rivaroxaban, apixaban). *Argatroban* has a U.S. Food and Drug Administration (FDA) indication for treatment heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT, see Chapter 68). Do not initiate acute PE therapy with the oral agents dabigatran and edoxaban, since they require at least 5 days of parenteral therapy (eg, UFH, LMWH, fondaparinux) before their initiation. Notably, most studies of anticoagulants for the indication of PE excluded ICU patients. Guidelines suggest using drugs other than UFH (eg, LMWH) for non–high-risk PE. Even though the oral agents apixaban and rivaroxaban have shown efficacy for the initial (and long-term) treatment of PE, we prefer to use parenteral agents for many ICU patients based on their shorter half-life, reversibility, lack of gastrointestinal (GI) absorption concerns, lower risk of drug interactions, and ability to monitor anticoagulant effect. Bleeding risk, likelihood of undergoing an invasive procedure, and possibility of receiving thrombolytic therapy often support use of parenteral over oral anticoagulant therapy in the ICU. Subcutaneously administered LMWH typically does not require

monitoring, and it has lower bleeding and HITT risks than IV UFH in non–ICU patients. However, in patients with high-risk acute PE, we prefer use of IV UFH over subcutaneous (SC) LMWH because of its better bioavailability during hypotension. With significant renal dysfunction, LMWH has decreased renal excretion, and its bleeding risk increases in comparison to UFH. Adjusted-dose anticoagulation (eg, UFH, direct thrombin inhibitors argatroban or bivalirudin) should undergo proper initial dosing and then timely titration to therapeutic levels to lower the risk of VTE recurrence or extension. For ICU patients treated with UFH for high-risk PE, and some patients with intermediate-risk PE, it might be prudent to check an activated partial thromboplastin time (aPTT) about 90 minutes after the UFH bolus. If the aPTT does not reach a very high value (eg, >150 seconds) in this setting, then another UFH bolus is indicated.

THROMBOLYTIC THERAPY

Thrombolytic agents convert plasminogen to plasmin and lead to rapid fibrin clot lysis. Thrombolytics may rapidly improve pulmonary perfusion, PH, RV function, and low systemic BP. The high risk of death in patients who have PE and associated hypotension or shock may indicate the need for treatment more aggressive than anticoagulation (ie, thrombolysis). Studies do not support the use of thrombolytic agents in most patients who have acute symptomatic PE (ESC low-risk and intermediate-risk PE). In the absence of large randomized clinical trials that demonstrate the benefits of thrombolytic therapy on mortality, the 2021 American College of Chest Physicians (ACCP) guidelines recommended the use of thrombolytic therapy for (1) patients with acute symptomatic PE and hypotension who do not have a high bleeding risk and (2) selected patients with acute symptomatic PE who deteriorate after starting anticoagulation and who have an acceptable bleeding risk. Thrombolysis has greatest efficacy when used soon after PE symptom onset and diagnosis, although may have efficacy through 14 days. More controversial indications for thrombolytic therapy for PE in normotensive patients consist of RV dysfunction, severe

hypoxemia, extensive embolic burden, saddle embolism, free floating right heart thrombus, and presence of a patent foramen ovale.

General contraindications to thrombolytic administration include active, recent, or high risk for bleeding (Table 16.2). Compared to UFH, thrombolytics for PE increase the major bleeding rate by 50% to 100%, from about 6% to 12% to about 9% to 22%, and they markedly increase the intracranial hemorrhage rate from less than 1% to about 1.5% to 3%.

TABLE 16.2 Contraindications to Thrombolytic Therapy

Absolute contraindications[a]
Serious active bleeding
Known major bleeding diathesis
History of intracranial hemorrhage
Known intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent nonhemorrhagic stroke (eg, within the past 3 mo)
Recent significant head trauma (eg, within the past 3 mo)
Recent intracranial or intraspinal surgery (eg, within the past 3 mo)
Suspected aortic dissection
Relative contraindications
Recent internal bleeding (eg, within the past 4 wk)
Recent major surgery (see aforementioned) or organ biopsy
Recent trauma (see aforementioned), including cardiopulmonary resuscitation (especially if prolonged)
Recent blood vessel puncture at noncompressible site
Platelet count <100,000/mm^3
Severe uncontrolled systemic hypertension
Diabetic retinopathy or other hemorrhagic ophthalmic conditions
Pregnancy
Acute pericarditis
Endocarditis
Significant hemostatic defects
Current use of long-acting anticoagulant with therapeutic dose or level
Advanced age (eg, greater than 75 y)
Prior stroke with residual neurologic deficits
Prior associated allergic reaction
Any other condition in which bleeding would be difficult to manage

[a]Some absolute contraindications (except concurrent intracranial hemorrhage) might not be “absolute” in the most extreme circumstances. Severity of condition and judgment of clinician will determine the categorization of absolute versus relative contraindications; list not all inclusive.

Types of thrombolytics include *selective*/*fibrin-specific* and *nonselective agents*. Fibrin-specific agents include recombinant tissue plasminogen activator (rtPA; ie, alteplase), its mutants, recombinant plasminogen activator (rPA; ie, reteplase), and tissue plasminogen activator (TNK-tPA; TNKase; ie, tenecteplase). Tenecteplase has a longer plasma half-life than reteplase, and alteplase has the shortest half-life. The previously used nonselective agents (urokinase and streptokinase) are no longer available for use in the United States. Studies have not demonstrated the superiority of one type of thrombolytic agent over another.

Of the thrombolytic agents, only alteplase has an FDA indication for acute PE (ie, massive PE). The standard alteplase dose for PE is 100 mg IV over 2 hours. For PE, **reteplase** is typically given as 10 U IV over 2 minutes, and 30 minutes later, another 10 U IV over 2 minutes. The tenecteplase dose for PE is 50 mg IV over 5 seconds for weight 90 kg or more, with a 5-mg downward dose adjustment for each 10 kg lower weight range, to 30 mg for weight below 60 kg. Some studies have proposed use of low-dose lytics (eg, alteplase 0.6 mg/kg [max dose 50 mg] IV over 15 minutes), especially in those who have a relative contraindication to or a less strong indication for lytic therapy, although controversy exists around such dosing. Relative contraindications, age, and body weight may affect decision-making regarding the use of standard-dose versus low-dose thrombolytic therapy. Regarding use of lytics during PE-associated cardiac arrest, small placebo-controlled studies have shown a higher rate of return of spontaneous circulation and perhaps survival after either alteplase 50 mg IV bolus or tenecteplase 50 mg IV bolus. Consider continuation of CPR, if needed, for up to 60 to 90 minutes after administration of thrombolytic drugs.

Some guidelines have differing recommendations regarding the use of anticoagulant therapy during thrombolytic therapy. Options

include discontinuation of anticoagulant therapy or using IV UFH (or possibly LMWH) during thrombolytic therapy. For the discontinuation strategy, after completion of thrombolytic therapy, the clinician should reinitiate UFH anticoagulation at the previous dose or start UFH, without a bolus, when the aPTT has decreased to less than 2 times the normal control value. Otherwise, the clinician should continue anticoagulation.

CATHETER-DIRECTED THERAPY

For patients who have acute PE-associated with hypotension (ESC high-risk PE) and a high bleeding risk or failed systemic thrombolysis, or shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), the CHEST 2021 guideline weakly recommended consideration of catheter-assisted thrombus treatment (catheter-directed therapy [CDT]) if appropriate expertise and resources are available. The ESC and the American Heart Association guidelines have similar recommendations regarding CDT.

CDT PE treatment options include endovascular fragmentation (eg, ultrasound, pressurized saline, rotational device, pigtail catheter rotation), aspiration of thrombus, catheter-directed thrombolytic therapy, and adjunctive balloon angioplasty. CDT studies have mainly shown improvements in RV size and function, with some showing improvements in clot burden and PA pressures. Types of complications similar among devices include distal embolization of thrombus, hypoxemia, elevation of PA pressure, and hemodynamic instability, and uncommonly PA perforation with (1) hemopericardium and pericardial tamponade, or (2) life-threatening hemoptysis, cardiac arrest, and death. Some device-specific complications may also occur, such as hemoglobinuria from red blood cell (RBC) fragmentation and bradycardia from adenosine released by disrupted platelets. Catheter-directed thrombolytic therapy, in comparison to systemic thrombolytic therapy, appears to have a lower risk of major systemic bleeding, including intracranial hemorrhage.

SURGICAL EMBOLECTOMY

Surgical embolectomy, at centers that have expertise, has a role in patients who have ESC high-risk PE, with proximal thrombi, and a contraindication to thrombolytic therapy or a failed thrombolytic therapy. Since the presence of extrapulmonary thrombi (eg, in the RA, RV, or vena cava) could alter surgical management, patients should undergo ECHO prior to and or during embolectomy. For failed thrombolytic therapy, surgical embolectomy has shown fewer recurrent PE and a trend toward fewer deaths in comparison to those who received repeat IV thrombolysis. Patients who have a right heart thrombus that straddles the interatrial septum via a patent foramen ovale/atrial septal defect might benefit from surgical embolectomy. Surgical embolectomy for free floating right heart thrombus remains controversial. Risks of surgical embolectomy include those associated with cardiac surgery, cardiopulmonary bypass and anesthesia, and embolectomy-specific complications such as PA perforation. Patients who have preoperative PE-associated cardiac arrest have high surgical and nonsurgical mortality.

INFERIOR VENA CAVA FILTERS

Studies have demonstrated a decreased risk of PE and an increased risk of DVT, without a significant effect on mortality, associated with IVC filter placement. IVC filters do not eliminate the risk of PE. Guidelines recommend that patients should undergo (temporary) IVC filter placement if they have a contraindication to anticoagulation, especially within the first month of therapy. If and when a reversible (eg, bleeding) contraindication to anticoagulation resolves, patients who have an IVC filter should undergo a standard course of anticoagulation and removal of the temporary filter. IVC filters have the risks of filter-associated thrombosis, IVC penetration and perforation, migration, tilt, and fracture. Recommendations vary regarding use of IVC filters in patients who develop VTE while receiving therapeutic anticoagulation.

RISKS OF TREATMENT

Bleeding

In general, ICU patients have a high risk of major bleeding because of coagulopathies, liver or renal insufficiency, significant comorbidities, increased risk for stress ulcers, and invasive procedures. Concomitant use of antiplatelet agents with anticoagulants increases the risk of bleeding (Table 16.3). For patients treated with thrombolysis (Table 16.2), prior stroke (especially if hemorrhagic, recent, or associated with residual neurologic deficits) has a significant risk for intracranial hemorrhage, recent major bleeding has a high risk of major bleeding at any site, and advanced age carries risk for both types of bleeding. Major bleeding should lead to the immediate discontinuation of all forms of anticoagulation/thrombolysis, appropriate monitoring, and supportive measures. Many scenarios may require blood product transfusion. Some scenarios require reversal of anticoagulant therapy (see Chapter 66).

TABLE 16.3 Bleeding Risk Factors[a] for Initial Anticoagulant Therapy

Risk Factors	
Age >65 y	Previous bleeding
Anemia	Thrombocytopenia
Coagulopathy	Renal failure
Liver failure	Recent surgery
Previous stroke	Cancer
Poor anticoagulant control	Antiplatelet therapy
Frequent falls	Comorbidity/reduced functional capacity

Risk Factors	
Alcohol abuse	Diabetes

Increased bleeding risk varies with (1) severity of the risk factor (eg, location and extent of metastatic disease, platelet count), (2) temporal relationships (eg, interval from surgery or a previous bleeding episode), and (3) previous effectiveness of correction of cause of bleeding (eg, upper gastrointestinal [GI] bleeding).

Compared with low-risk patients (0 risk factors), moderate-risk patients (1 risk factor) have a 2-fold risk, and high-risk patients (≥2 risk factors) have an 8-fold risk of major bleeding.

[a]List not all inclusive.

Adapted from Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e432 (Table 2).

Heparin-Induced Thrombocytopenia

Clinicians should consider the possibility that HITT (see Chapter 68) has occurred in patients who develop VTE in the setting of absolute or relative thrombocytopenia. Patients receiving UFH or LMWH should undergo monitoring for HIT. Patients who have PE and suspected or confirmed HIT should not receive UFH, LMWH, or warfarin until the HIT has resolved. Such patients should undergo treatment with a direct thrombin inhibitor such as argatroban or bivalirudin (see Chapter 68).

SUGGESTED READINGS

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Konstantinides S, Geibel A, Heusel G, et al; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase

17 Pleural Disorders in the Intensive Care Unit

Max Wayne and Alexander C. Chen

Disorders of the pleura are found often in the intensive care unit (ICU). In some instances, pleural processes may be the primary cause of patients' critical illness; in most cases, pleural disorders are recognized as secondary processes related to patients' underlying illness. This chapter will review the pathophysiology of these disorders and provide guidelines for managing these conditions in the ICU.

Pleural Effusions

The pleural space is a potential space between the visceral pleura, which covers the outer surface of the lung, and the parietal pleura, which lines the inside of the chest wall. In this space, there is a small amount of fluid present that functions to mechanically couple the lung to the chest wall and lubricate the interface of the visceral and parietal pleura. Pleural fluid normally results from the filtration of blood through high-pressure systemic blood vessels and is drained from the pleural space through lymphatic openings in the parietal pleura that drain into parietal lymphatic vessels. In different disease states, fluid may originate from the interstitial spaces of the lungs, the intrathoracic lymphatics, the intrathoracic blood vessels, or the peritoneal cavity.

A pleural effusion is defined as an abnormal collection of fluid in the pleural space. Effusions occur when the rate of fluid formation exceeds the rate of fluid absorption. The most common causes of pleural effusions are shown in Table 17.1. Pleural effusions are

commonly classified as being either exudative or transudative. An exudative pleural effusion implies that there is a disease process that is affecting the pleura directly, causing the pleura and/or its vasculature to be damaged. A transudative pleural effusion results when the pleura itself is healthy and implies that a disease process is affecting hydrostatic and/or oncotic factors that either increase the formation of pleural fluid or decrease the absorption of pleural fluid. Deciding if the pleura is injured or intact helps in formulating a concise differential diagnosis for potential causes (Table 17.2).

TABLE 17.1 Common Causes of Pleural Effusions

CHF, 36%
Pneumonia, 22%
Malignancy, 14%
Pulmonary embolism, 11%
Other infections, 7%
Other causes, 10%

CHF, congestive heart failure.

TABLE 17.2 Pathophysiologic Causes of Pleural Effusions

How Pleura Are Affected	Example	Exudate/Transudate
Pleura damaged		
Local disease in pleural space	• Malignancy	• Exudate
• Local disease adjacent to pleural space	• Pneumonia, PE, subdiaphragmatic abscess	• Exudate
• Systemic diseases that affect the pleural surface	• Autoimmune disease (lupus, rheumatoid arthritis)	• Exudate

How Pleura Are Affected	Example	Exudate/Transudate
Pleura intact		
• Systemic disease that does not directly affect the pleural surface	• CHF, myxedema, cirrhosis	• Transudate

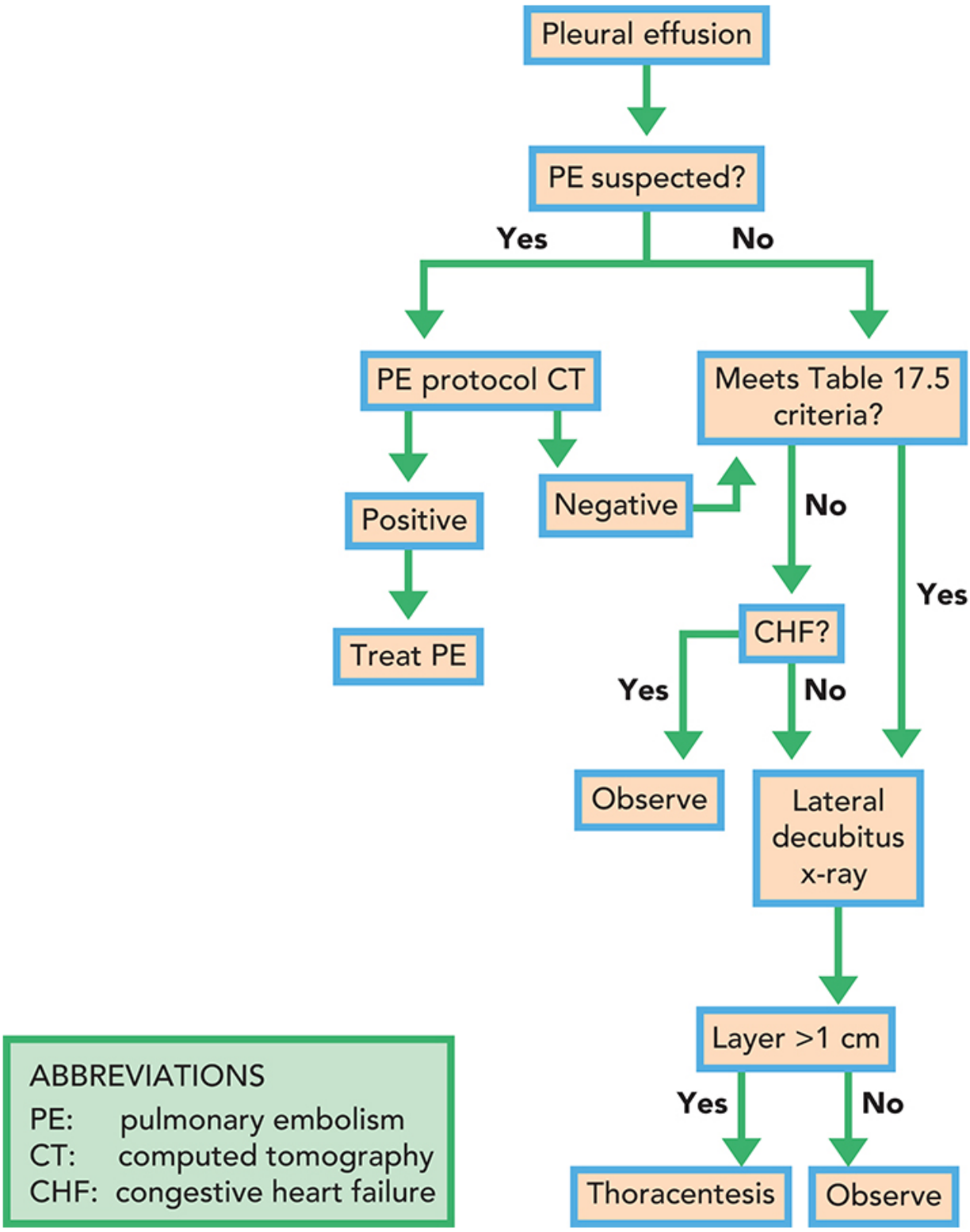
CHF, congestive heart failure; PE, pulmonary embolism.

There are certain nonspecific signs and symptoms that may indicate the presence of a pleural effusion, but these are often difficult to ascertain in the ICU. Chest pain, particularly when sharp and made worse with breathing, can result from inflamed pleura in the presence of an effusion. Dyspnea is also common as the effusion can affect the mechanics of the diaphragm, cause a restrictive ventilatory defect, and/or cause compressive atelectasis leading to hypoxemia. The history can also help to reveal the cause of the effusion. For example, a patient with a fever and cough productive of sputum might have pneumonia causing the effusion. On physical examination, signs that an effusion is present include dullness to percussion over the effusion, loss of fremitus, decreased breath sounds, crackles/egophony immediately above the effusion, and asymmetric diaphragmatic excursion with inspiration.

The majority of ICU patients will have their pleural effusion detected first by chest x-ray. Although a posterior-anterior (PA) and lateral chest x-ray is the preferred image, ICU patients typically have portable x-rays. Blunting of the costophrenic angle and a meniscus sign are the most common findings when an effusion is present. On the lateral chest x-ray, as little as 175 mL of fluid can be detected, while on the PA film, it takes approximately 500 mL of fluid. Portable films are less sensitive and often do not show the meniscus sign. Signs on the portable chest x-ray include loss of the diaphragm silhouette and increased basilar opacity with gradation over the entire hemithorax (more opaque at the base than the apex). Once a pleural effusion is detected radiographically, a lateral decubitus chest x-ray (where the dependent side is the side of the effusion) can

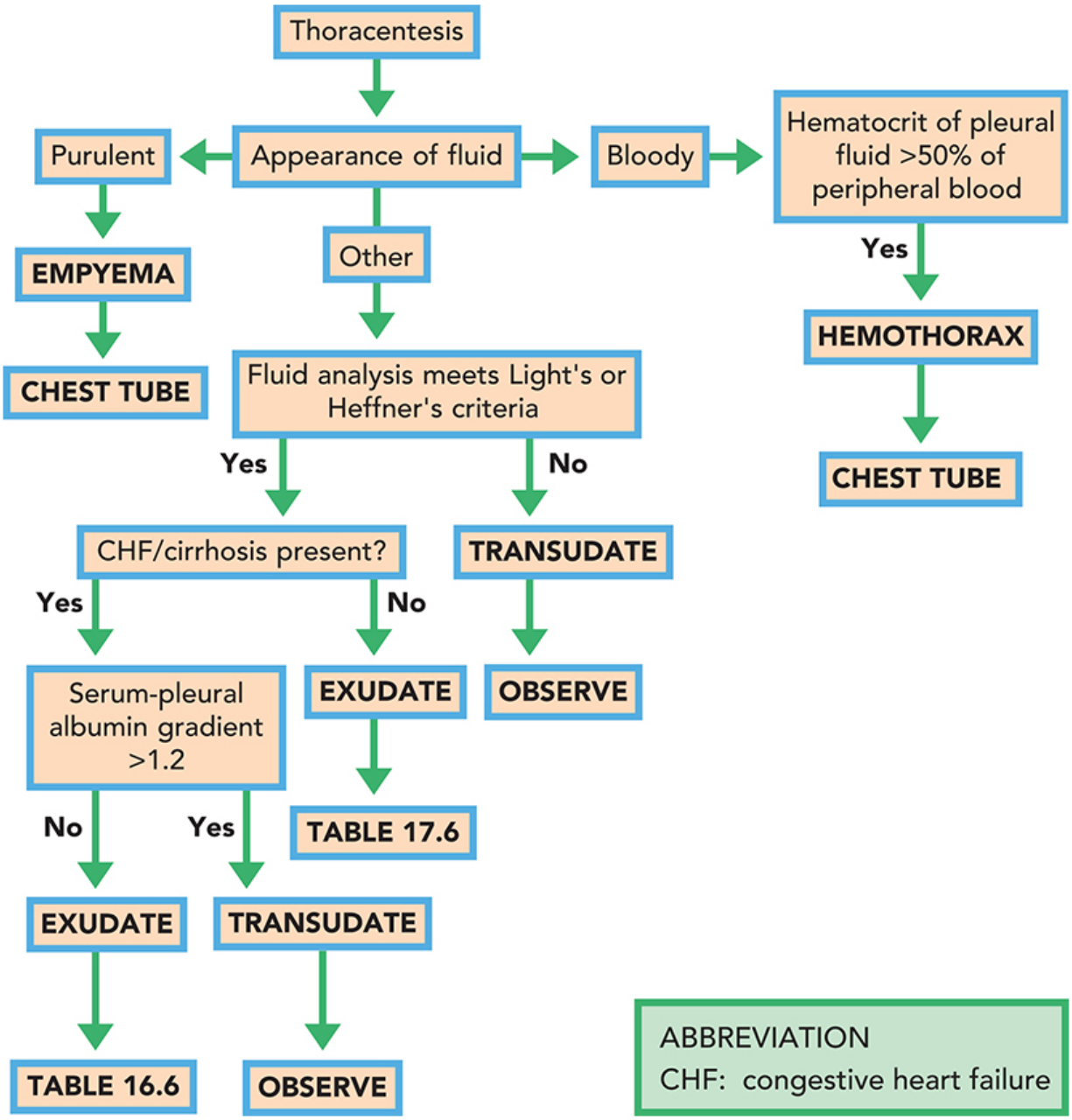
quantitate the volume of fluid present and determine if the effusion is free-flowing or loculated. If the fluid is free-flowing, fluid can be detected as a straight line between the chest wall and the lower border of the lung. Measurement of the distance between the chest wall and the lower border of the lung can give an idea of how much fluid is present. It is generally accepted that if this distance is more than 1 cm, then the amount of fluid is significant. Diagnostic evaluation of the effusion from this point is discussed in Algorithms 17.1 and 17.2.

ALGORITHM 17.1 Evaluation of the Unknown Effusion



90% of pleural effusions are caused by five processes, as shown in Table 17.1.

ALGORITHM 17.2 **Evaluation and Management of Pleural Fluid After Thoracentesis**



From Colice GL. Medical and surgical treatment of parapneumonic effusions. *Chest*. 2000;118:1161, with permission.

Other imaging modalities can also detect, quantify, and, sometimes, even characterize the pleural effusion. Ultrasound is

beneficial for multiple reasons. It gives a real-time image that can be done at the bedside and can be used not only for diagnosis that an effusion is present but also guide diagnostic and therapeutic interventions (ie, thoracentesis, tube thoracostomy). Ultrasound can detect whether the fluid is loculated or free-flowing and can give clues as to whether the fluid is transudative, exudative, or even whether it is an empyema.

Chest computed tomography (CT) is a useful imaging tool in assessing pleural effusions and can help the clinician diagnose not only the presence of the effusion but also delineate possible causes. Different techniques yield different information; therefore, it is important to select the appropriate technique.

- Noncontrast CT scans can give a better idea of the amount of fluid within the pleural space, whether the fluid is loculated, and can detect abnormalities in the lungs that can be obscured by the effusion on standard chest x-ray.
- Standard contrast CT scans also assess the pleural surface for abnormalities that might suggest empyema or pleural malignancy.
- CT scans with contrast given by pulmonary embolism protocol can detect a pulmonary embolism as the cause of the effusion but do not provide information about the pleural surface beyond that of a noncontrast CT.

CT scans cannot be done at bedside, a big disadvantage when dealing with a patient who is not stable enough to travel out of the ICU.

Once a pleural effusion is identified, it is important to attempt to diagnose the etiology of the effusion by obtaining a sample of the fluid for analysis. This is most often done by a thoracentesis. Thoracenteses can be safely performed as long as there is more than 2 cm of fluid on ultrasound, even in patients receiving mechanical ventilation. One can remove a small amount of fluid for analysis or more than 1,500 mL for both diagnostic and therapeutic goals (Algorithms 17.2-17.4). The most common criteria used to separate exudates from transudates are Light’s criteria (Table 17.3).

Heffner's criteria (Table 17.4) can also differentiate exudate from transudate. Heffner's criteria have a similar sensitivity (98.4%) as Light's criteria (97.9%) and do not require simultaneous blood work to be drawn.

TABLE 17.3 Light's Criteria

Pleural fluid to serum protein ratio >0.5
Pleural fluid to serum LDH ratio >0.6
Pleural fluid LDH >2/3 upper limit of normal for serum LDH

LDH, lactate dehydrogenase.

TABLE 17.4 Heffner's Criteria

Pleural fluid protein >2.9 g/dL
Pleural fluid LDH >0.45 upper limit of normal

LDH, lactate dehydrogenase.

Other specific tests (Tables 17.5 and 17.6) can help determine a specific diagnosis.

TABLE 17.5 Indications for Thoracentesis

Pleural effusion of unknown etiology
Fever in the setting of long-standing pleural effusion
Air-fluid level in the pleural space
Rapid change in size of effusion
Concern that empyema is developing

TABLE 17.6 Diagnostic Tests to Consider in Evaluation of Pleural Effusions

Diagnostic Test	Type of Effusion

Diagnostic Test	Type of Effusion
Cytology	Malignant effusion
Gram stain or culture positive	Infectious effusion (ie, bacterial, fungal)
AFB positive; pleural fluid ADA >70 U/L	Tuberculous effusion
Rheumatoid arthritis cells	Rheumatoid effusion
Chylomicrons present; pleural fluid triglycerides >110 mg/dL	Chylothorax
Salivary amylase present in pleural fluid	Esophageal rupture
Pleural creatinine/serum creatinine >1	Urinothorax

ADA, adenosine deaminase; AFB, acid-fast bacillus.

As many as 20% of pleural effusions remain undiagnosed even after extensive investigation, and it is often unclear as to what the appropriate management of these effusions is in these situations. These idiopathic effusions with no clinical or radiologic evidence of malignancy will often resolve spontaneously without further therapy. In the ICU setting, as long as the patient does not clinically deteriorate, a conservative approach may be preferred when a diagnosis cannot be made after initial evaluation. If the patient continues to deteriorate despite serial thoracenteses, thoracoscopy can be considered as the next step to assess the pleural effusion.

Special Situations

PARAPNEUMONIC EFFUSION

A parapneumonic effusion is defined as any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis. Parapneumonic effusions progress through different

stages, and depending on when the patient presents, the treatment of the effusion will be different. The main distinction is whether the effusion is uncomplicated or complicated. Complicated effusions and empyemas will not resolve on their own and will require tube thoracostomy. As shown in Algorithm 17.3 and Table 17.7, radiographic, microbiologic, and chemical characteristics of the effusion will dictate whether thoracentesis with antibiotics alone will be sufficient to treat the effusion or whether a chest tube must be inserted to effectively treat the effusion. The use of intrapleural fibrinolytics and DNase twice a day for 3 days has been shown to improve pleural fluid drainage, reduce the need for surgical therapy, and decrease length of hospital stay when compared to either therapy alone. If intrapleural therapy is unsuccessful, the patient may require more invasive therapy, including thoracoscopy with breakdown of adhesions or thoracotomy with decortication.

ALGORITHM 17.3 Management of Parapneumonic Effusions

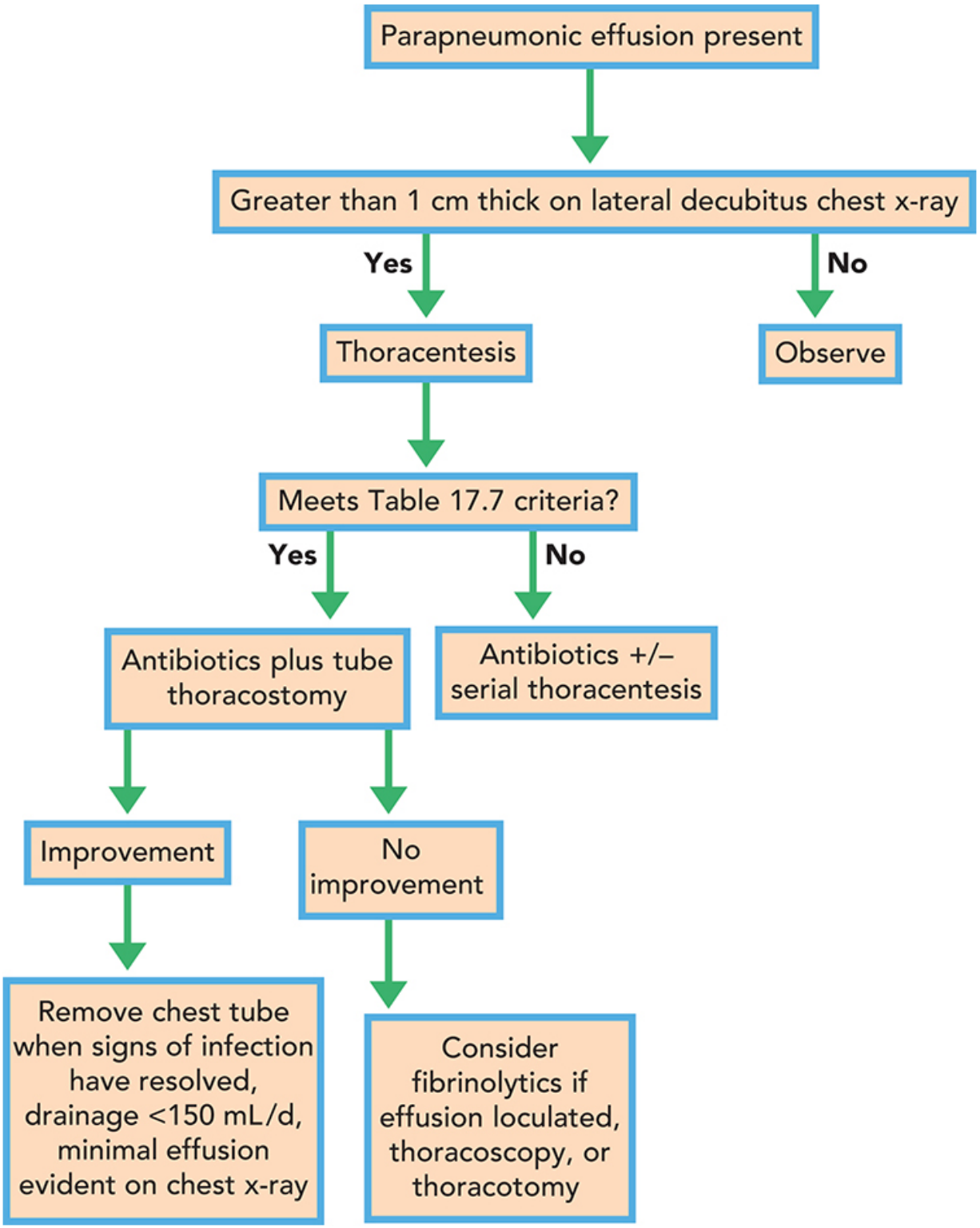

Parapneumonic effusion present
Greater than 1 cm thick on lateral decubitus chest x-ray
Yes
No
Thoracentesis
Observe
Meets Table 17.7 criteria?
Yes
No
Antibiotics plus tube thoracostomy
Antibiotics +/– serial thoracentesis
Improvement
No improvement
Remove chest tube when signs of infection have resolved, drainage <150 mL/d, minimal effusion evident on chest x-ray
Consider fibrinolytics if effusion loculated, thoracoscopy, or thoracotomy

TABLE 17.7 **Indication for Tube Thoracostomy in Parapneumonic Effusions**

1. Radiographic
    - Pleural fluid loculation
    - Effusion filling more than half of hemithorax
    - Air-fluid level present
2. Microbiologic
    - Pus in pleural space
    - Positive Gram stain for microorganisms
    - Positive pleural fluid cultures
3. Chemical
    - Pleural fluid pH < 7.2
    - Pleural fluid glucose < 60

MALIGNANT EFFUSION

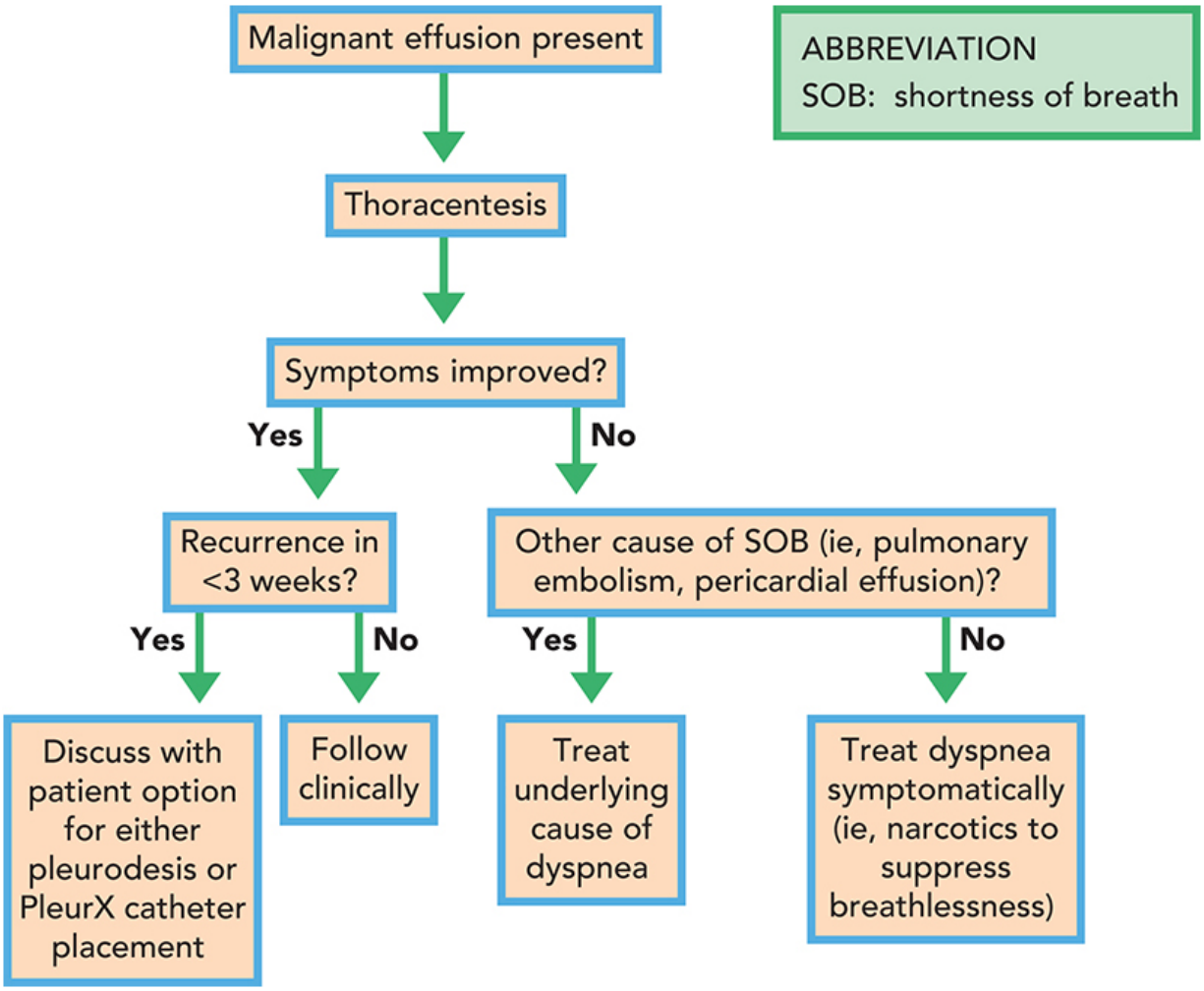
Malignant pleural effusions occur from a number of causes. Pleural metastases occur causing increased permeability of the pleura, and lymphatic obstruction can occur, which impairs drainage of pleural fluid through regional lymphatics. Table 17.8 shows the most common malignancies associated with pleural effusions. When these effusions occur, they are often large and lead to significant symptoms in the patient. Often, drainage of the effusion with thoracentesis alone is not sufficient as the effusion frequently recurs. Other management options include insertion of a chest tube followed by pleurodesis, which can obliterate the pleural space and prevent the effusion from recurring. Alternatively, insertion of a long-term indwelling catheter will allow the patient to drain the effusion at home and is a viable option that decreases hospitalizations and increases the quality of life of the patient. Additionally, these indwelling catheters can be attached to Pleur-evac systems and used as chest tubes to support patients through their period of critical illness. Once in place, these catheters can be managed similarly to traditional tube thoracostomies. Management of this type of effusion is outlined in Algorithm 17.4.

TABLE 17.8 Most Common Primary Tumors of Malignant Effusions

Primary Malignancy	Rate (%)
Lung	38
Breast	17
Lymphoma	12
Unknown primary	11
GU tract	9
GI tract	7

GI, gastrointestinal; GU, genitourinary.

ALGORITHM 17.4 Management of Recurrent Malignant Effusions



Reproduced from Antunes G, Neville E, Duffy J, et al. BTS guidelines for the management of malignant pleural effusions. *Thorax*. 2003;58(suppl II):ii30,with permission from BMJ Publishing Group Ltd.

HEMOTHORAX

A hemothorax is the presence of blood in the pleural space such that the ratio of pleural fluid hematocrit to blood hematocrit is greater than 0.5. This can be a serious condition and may result in ICU admission for treatment. Hemothoraces can be due to traumatic, nontraumatic, or iatrogenic causes (Table 17.9). Diagnosis is made after a thoracentesis returns bloody fluid (Algorithm 17.2). It should be noted that even a small amount of blood can make pleural fluid appear bloody; therefore, the fluid's hematocrit needs to be

compared with peripheral blood hematocrit to confirm the presence of a hemothorax. Initial treatment for hemothoraces of all causes is tube thoracostomy. If bleeding is voluminous and persists, transfusion and either interventional radiologic or surgical intervention may be required.

TABLE 17.9 Causes of Hemothoraces

Causes	Examples
Traumatic	Penetrating trauma (gunshot wound), blunt trauma (usually with displaced rib fracture)
Nontraumatic	Metastatic malignant pleural disease, complication of anticoagulant therapy for pulmonary emboli
Iatrogenic	Perforation of a central vein from percutaneous catheter placement, following thoracentesis, following pleural biopsy

PNEUMOTHORAX

A pneumothorax is the presence of air in the pleural space. When this occurs, it can be an acute emergency that requires immediate attention. A pneumothorax can be spontaneous or traumatic. Spontaneous pneumothoraces are either primary, if no other disease process is present, or secondary, if there is an underlying disease process such as chronic obstructive pulmonary disease. Traumatic pneumothoraces include iatrogenic causes that may occur following a procedure (ie, central line placement) or barotrauma. Primary spontaneous and traumatic pneumothoraces can often be treated effectively with observation or tube thoracostomy. Secondary spontaneous pneumothoraces typically require tube thoracostomy and may also require pleurodesis for definitive treatment.

Tension pneumothorax is the most serious consequence of a pneumothorax. This occurs when a one-way valve process develops, which allows air to enter the pleural space during

inspiration but not leave during expiration. As the air builds up in the pleural space, the lung and intrathoracic vasculature become compressed, leading to dyspnea, hypoxemia, and hemodynamic compromise. Physical examination may reveal the absence of breath sounds on the side of the pneumothorax and/or a shift of the trachea to the contralateral side of the pneumothorax. Tension pneumothorax should be suspected in unstable patients with absent breath sounds over one hemithorax, in mechanically ventilated patients who suddenly decompensate, in patients with known previously stable/improving pneumothorax who suddenly decompensate, or in patients who become unstable during or after a procedure known to cause a pneumothorax. Algorithm 17.5 gives further information on the evaluation and management of pneumothoraces. Table 17.10 covers the indications for removal of the chest tube.

ALGORITHM 17.5 Management of Pneumothorax

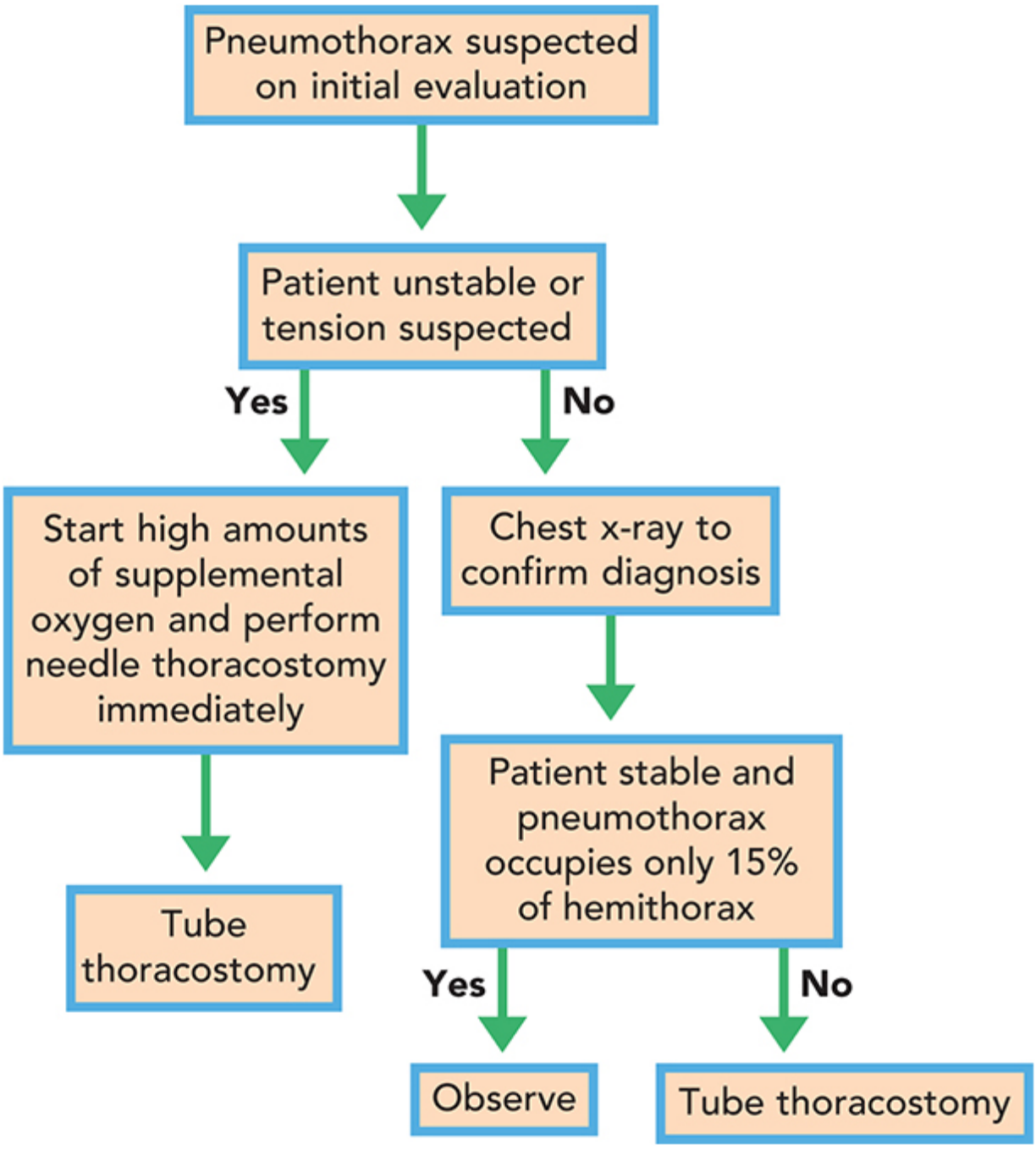


TABLE 17.10 Indications for Removal of Chest Tube

1. Pneumothorax resolved
2. No air leak present in chest tube
3. Lung remains expanded after chest tube placed on water seal for 24 h

If concern remains, chest tube can be clamped for 4 to 8 hours followed by chest radiograph; if lung expanded, then it is safe to remove the chest tube.

Treatment of a persistent pneumothorax (air leak > 72 hours) or a bronchopleural fistula is difficult, requires a multidisciplinary approach, and leads to considerable patient morbidity and mortality. The most common cause is postoperative pulmonary resection with other less common causes, including necrotizing lung infections, trauma, rupture of lung bullae, or iatrogenic causes. The two main treatment options are surgical repair or endoscopic management. Endoscopic options include tissue sealants, glue, silver nitrate injections, endobronchial stents, occlusion coils, and one-way valves. In carefully selected patient populations, one-way valves can be successful in resolving persistent air leaks but require localized injury to the lung that can be identified with bronchoscopy with balloon occlusion. In cases with diffuse injury to the lung, endoscopic management is unlikely to be successful.

CHEST TUBE SIZE

The optimal size of chest tube for treating pleural disease has not been evaluated in prospective randomized trials. A clear advantage for small-bore chest tubes (≤14 French) are ease of insertion with the Seldinger technique (compared to blunt dissection with large tubes), less pain for the patient, and lower risk of procedural complications. Small-bore chest tubes are recommended for pleural drainage of fluid or air in the majority of patients. The British Thoracic Society guidelines state small-bore chest tubes (10-14 French) with regular flushing will be adequate for most cases of pleural infection. Hemothorax may be better managed with large-bore chest tubes (>14 French) to allow for complete drainage, although there is more limited data to suggest that even in traumatic hemothorax, small-bore chest tubes may be sufficient. In cases where residual effusion remains, there may be a role for intrapleural lytics to facilitate clearance of residual effusion.

18 Weaning of Mechanical Ventilation

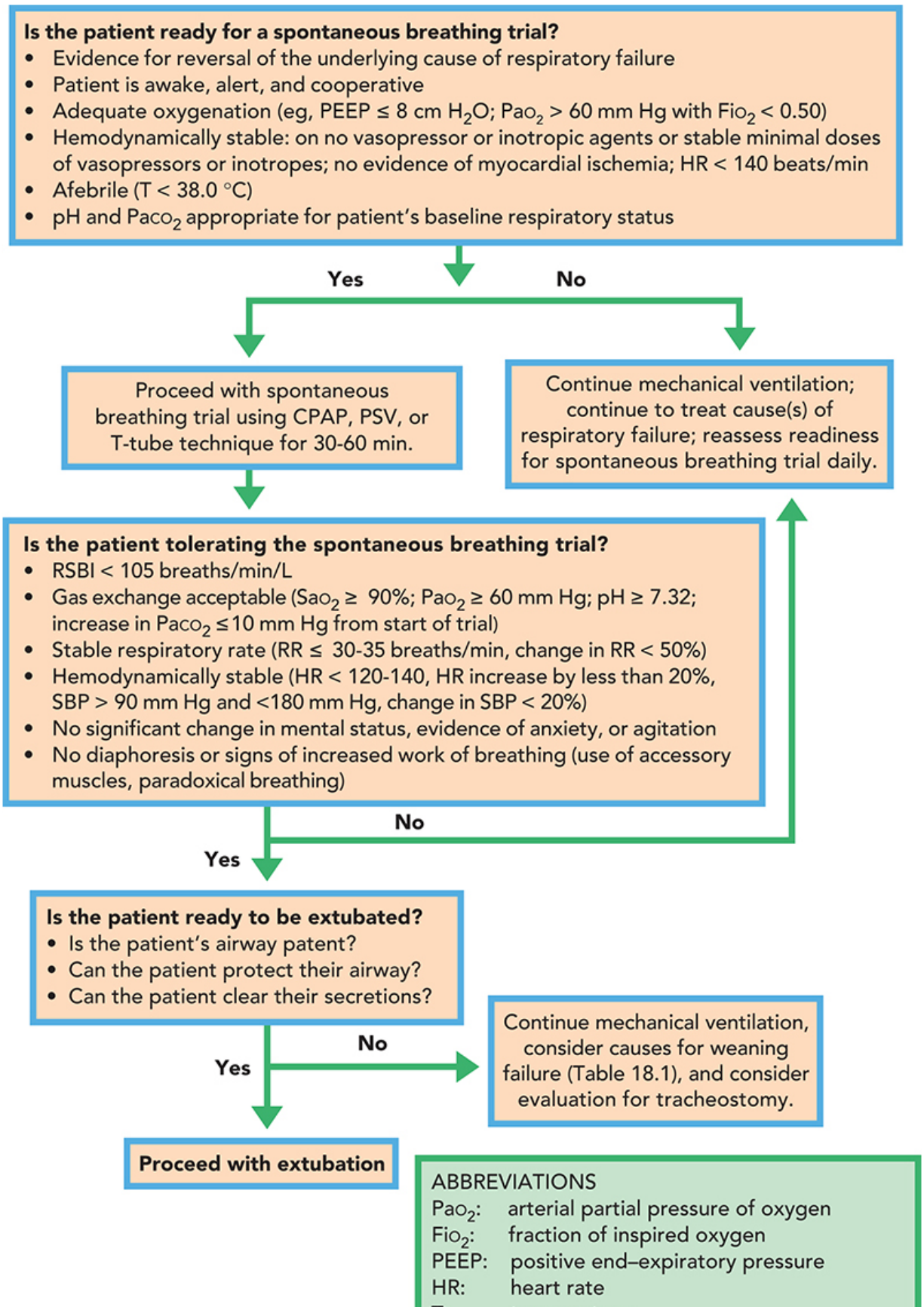
Rachel K. McDonald

Intubation for airway protection and respiratory failure is common in the intensive care unit (ICU). It is estimated that 800,000 patients are intubated annually in the United States. The complications of mechanical ventilation include infection, airway trauma, and ICU-acquired weakness due to immobilization. For this reason, it is important to proceed with mechanical ventilation withdrawal as quickly as the patient will tolerate. The gradual withdrawal of mechanical ventilation is termed *weaning.* Weaning can be divided into two components: (a) *liberation*, which entails no longer requiring mechanical ventilatory support, and (b) *extubation/decannulation*, referring to the removal of the endotracheal or tracheostomy tube. While the weaning of mechanical ventilation in the ICU setting for acute respiratory failure is discussed later, prolonged ventilator weaning after severe chronic illness is beyond the scope of this chapter.

Mechanical ventilation weaning is a sequential process. First, the underlying disease process causing the patient's initial respiratory failure must be significantly improved or resolved. Second, the patient must be awake, able to cooperate, hemodynamically stable, and capable of coughing and protecting the airway. Minimal ventilator settings with positive end–expiratory pressure (PEEP) less than or equal to 8 cmH_2O and F_{IO_2} less than or equal to 50% are ideal. Other parameters, such as negative inspiratory force, should be assessed in selected patients, including those with underlying neuromuscular disease. Patients should be on no or minimal stable dose of vasopressor therapy. Third, daily spontaneous awakening trials (SATs) should be performed during which sedation is stopped

or reduced. An SAT is successful if the patient has stable respiratory parameters and hemodynamics and is able to remain calm on minimal or no sedation. If an SAT is successful and the patient is on minimal ventilator settings, a spontaneous breathing trial (SBT) should be initiated. Patients who are intubated on mechanical ventilation should be evaluated for readiness to undergo an SBT on a daily basis (Algorithm 18.1). Protocols combining daily SAT and SBT driven by nurses and respiratory therapists have been shown to decrease duration of mechanical ventilation.

ALGORITHM 18.1 **Readiness to Liberate and Wean From Mechanical Ventilation**


Is the patient ready for a spontaneous breathing trial?
• Evidence for reversal of the underlying cause of respiratory failure
• Patient is awake, alert, and cooperative
• Adequate oxygenation (eg, PEEP ≤ 8 cm H_2O; Pao_2 > 60 mm Hg with Fio_2 < 0.50)
• Hemodynamically stable: on no vasopressor or inotropic agents or stable minimal doses of vasopressors or inotropes; no evidence of myocardial ischemia; HR < 140 beats/min
• Afebrile (T < 38.0 °C)
• pH and $Paco_2$ appropriate for patient's baseline respiratory status
Yes
No
Proceed with spontaneous breathing trial using CPAP, PSV, or T-tube technique for 30-60 min.
Continue mechanical ventilation; continue to treat cause(s) of respiratory failure; reassess readiness for spontaneous breathing trial daily.
Is the patient tolerating the spontaneous breathing trial?
• RSBI < 105 breaths/min/L
• Gas exchange acceptable (Sao_2 ≥ 90%; Pao_2 ≥ 60 mm Hg; pH ≥ 7.32; increase in $Paco_2$ ≤ 10 mm Hg from start of trial)
• Stable respiratory rate (RR ≤ 30-35 breaths/min, change in RR < 50%)
• Hemodynamically stable (HR < 120-140, HR increase by less than 20%, SBP > 90 mm Hg and <180 mm Hg, change in SBP < 20%)
• No significant change in mental status, evidence of anxiety, or agitation
• No diaphoresis or signs of increased work of breathing (use of accessory muscles, paradoxical breathing)
No
Yes
Is the patient ready to be extubated?
• Is the patient's airway patent?
• Can the patient protect their airway?
• Can the patient clear their secretions?
No
Yes
Continue mechanical ventilation, consider causes for weaning failure (Table 18.1), and consider evaluation for tracheostomy.
Proceed with extubation
ABBREVIATIONS
Pao_2: arterial partial pressure of oxygen
Fio_2: fraction of inspired oxygen
PEEP: positive end–expiratory pressure
HR: heart rate

T:	temperature
$Paco_2$:	arterial partial pressure of carbon dioxide
CPAP:	continuous positive airway pressure
PSV:	pressure support ventilation
RSBI:	rapid shallow breathing index
Sao_2:	arterial oxygen saturation
RR:	respiratory rate
SBP:	systolic blood pressure

There are multiple weaning strategies and SBT protocols that have been studied and utilized. SBTs can be done using pressure support ventilation (PSV), continuous positive airway pressure (CPAP), or T-tube technique. Using PSV, a pressure support of 5 to 10 cm H_2O is delivered to help the patient overcome the resistance of the endotracheal tube, usually accompanied by a PEEP of 8 cm H_2O or less. During a CPAP trial, 5 cm H_2O of CPAP is often provided. Lastly, the T-tube technique provides oxygen flow without any pressure support or CPAP during the trial. The head of the bed should be elevated 30 to 60 degrees to optimize diaphragmatic mechanics during the trial.

The three aforementioned SBT modalities (PSV, CPAP, or T-piece) have been studied rigorously to determine which modality is superior to determine readiness for extubation. Overall, patients who underwent SBT with PSV trials were just as if not more likely to successfully extubate as those who underwent SBT with T-piece trails. Additionally, those who underwent T-piece trials were more likely to fail the SBT. Therefore, PSV is the most often used modality for spontaneous breathing trials. A quick physical assessment should be done before and after each SBT to assess hemodynamic parameters and overall patient comfort during the SBT. The patient should be monitored for evidence of SBT failure as well as markers of successful SBT completion. A useful measure in determining extubation readiness is the rapid shallow breathing index (RSBI), defined as the respiratory rate/tidal volume (f:V_t ratio). A rapid shallow breathing index of less than 105 breaths/min/L during an SBT indicates that a patient is more likely to be successfully extubated. While the RSBI is helpful, it should not be used as the

sole method to evaluate readiness for extubation. During a successful trial, a patient will also demonstrate pulmonary and hemodynamic stability (respiratory rate less than 35 per minute, minimal change in heart rate, blood pressure, and oxygen saturations, minimal anxiety, and no increase in work of breathing). In addition to the modality chosen, the appropriate duration of SBT has also been debated. SBT duration of 30 minutes has been shown to be at least equivalent to predicting extubation success when compared with longer SBT trials in the majority of patients, supporting the recommendation for shorter SBT trials as an evaluation for extubation readiness.

The widespread use of bedside ultrasound in the critical care setting has led to the use of ultrasound to aid in predicting extubation success. Cardiac parameters, including diastolic dysfunction and elevated left ventricular filling pressure measured by the E/e' ratio have been associated with SBT failure. In addition, the lung ultrasound score (LUS), diaphragm excursion, and diaphragm thickening fraction have also been shown to predict extubation outcomes.

Difficult-to-wean patients are those who do not wean from mechanical ventilation within 48 to 72 hours of resolution of their underlying disease process. In such patients, the acronym "WEANS NOW" has been developed as a set of factors to be considered in difficult-to-wean patients (Table 18.1).

TABLE 18.1 Issues to Be Considered When Weaning Efforts Fail

Weaning parameters (see Algorithm 18.1)
Endotracheal tube
Use the largest tube possible
Consider use of supplemental pressure support ventilation during spontaneous breathing trial

- Suction secretions

Arterial blood gases

- Avoid or treat metabolic alkalosis
- Maintain Pa_{O_2} at 60-65 mm Hg to avoid increased shunt in patients with chronic CO_2 retention
- For patients with CO_2 retention, keep Pa_{CO_2} at or above the baseline level

Nutrition

- Ensure adequate nutritional support
- Avoid electrolyte deficiencies
- Avoid excessive calories

Secretions

- Clear regularly
- Avoid excessive dehydration

Neuromuscular factors

- Avoid neuromuscular depressing drugs (neuromuscular blockers, aminoglycosides, clindamycin) in patients with muscle weakness
- Avoid unnecessary corticosteroids

Obstruction of airways

- Use bronchodilators when appropriate
- Exclude foreign bodies within the airway

Wakefulness

- Avoid oversedation

Wean in morning or when patient is most awake

From Kollef MH. Critical care. In: Green GB, Harris IS, Lin GA, et al., eds. *The Washington Manual of Medical Therapeutics*. 31st ed. Lippincott Williams & Wilkins; 2004:192.

A successful SAT/SBT should prompt extubation. Prior to extubation, the endotracheal tube and airways should be suctioned to clear secretions. A cuff leak test can be performed if there is a concern for laryngeal edema. A decreased or absent cuff leak has been shown to predict laryngeal edema, although the definition of a "normal" cuff leak is variable among studies. Patients who develop laryngeal edema and postextubation stridor may need reintubation; therefore, consideration should be given to treatment with corticosteroids when a cuff leak is decreased or absent. Corticosteroid regimens with multiple doses or doses given more than 4 hours before extubation have the most effect on decreasing laryngeal edema.

After extubation, most patients can be safely transitioned to nasal cannula oxygen. Some patients may benefit from or require noninvasive positive pressure ventilation (NIPPV) after extubation, particularly those with chronic hypercapnia or congestive heart failure. More recently, the use of humidified high-flow nasal cannula (HHFNC) immediately after extubation has been shown to improve outcomes when compared with lesser oxygen supplementation and could be considered as an oxygen supplementation strategy after extubation. Patients should be asked to cough several times within the first few minutes of extubation to clear any secretions. It should be kept in mind that there will be extubation failures in patients who are deemed ready by all objective evaluations (reported reintubation rates 11%-23.5%); these patients may benefit from early tracheostomy. Given this risk of recurrent respiratory failure, patients should be monitored in the ICU for a period of time in order to ensure reintubation is not required.

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19 Noninvasive Ventilation

Robert Case and Adam Anderson

Noninvasive ventilation (NIV) delivers mechanically assisted breaths using tight-fitting masks or interfaces, all with separate benefits and limitations (Table 19.1). NIV may prevent the need for endotracheal intubation, but requires optimal patient selection and frequent reevaluation. The correct NIV mode and patient-tailored settings are imperative for success.

TABLE 19.1 Types of Masks/Interfaces

Interface	Advantages	Disadvantages
Nasal pillow	• Improved patient comfort • Able to speak and swallow during use	• Air leaks from the uncovered mouth • Not advised for use during acute respiratory failure
Nasal mask	• Improved patient comfort • Able to speak and swallow during use	• Air leaks from the uncovered mouth • Not advised for use during acute respiratory failure • Potential for cutaneous breakdown at nasal bridge
Full face mask (oronasal mask)	• Better for mouth breathers • Mask of choice for initiation of NIV	• Potential for cutaneous breakdown at nasal bridge • Limited use in claustrophobic patients

Interface	Advantages	Disadvantages
Total face mask	• Better for mouth breathers • Easier use for patients with facial irregularities • No pressure applied to nasal bridge	• Limited use in claustrophobic patients
Helmet	• Better for mouth breathers • Easier use for patients with facial irregularities • More comfortable seal • Diminished leaks	• Carbon dioxide accumulates in helmet • New technology with limited experience among providers

NIV, noninvasive ventilation.

Patient Selection

Although NIV can be used in several situations, appropriate selection is necessary for optimal outcomes. Broadly, NIV can be considered in patients with either hypoxemic or hypercarbic respiratory failure, especially if the clinical deterioration is felt to be rapidly reversible. The best evidence to support its use is with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and acute cardiogenic pulmonary edema, though the use of NIV is frequently extended to additional patients.

Equally important are contraindications to trials of NIV. Generally accepted absolute contraindications include inability to fit the NIV mask appropriately, cardiopulmonary arrest, and need for urgent intubation. There are several relative contraindications; most commonly encountered relative contraindications include encephalopathy with inability to protect ones airway,

uncooperativeness, and claustrophobia. Additional relative contraindications are provided in Table 19.2.

TABLE 19.2 Relative Contraindications to NIV

Shock/hemodynamic instability	Facial surgery, trauma, or deformity
Claustrophobia/anxiety	Upper airway obstruction
Encephalopathy	Inability to protect airway
Upper gastrointestinal bleeding	High risk for aspiration
Unstable cardiac rhythm	Inability to clear secretions

NIV, noninvasive ventilation.

The advantages of NIV over invasive mechanical ventilation (IMV) have resulted in its widespread implementation over a variety of clinical scenarios. In general, patients experiencing hypoxemia, hypercapnia, or respiratory muscle fatigue without absolute or relative contraindications warrant a trial of NIV.

MODES

Once the decision to initiate NIV is made, the optimal mode and settings must be considered. A simplified approach to understanding different NIV options is to differentiate by settings available for manipulation. Common modes of NIV are summarized in Table 19.3, with benefits and limitations emphasized.

TABLE 19.3 Common Modes of NIV

CPAP	BiPAP	AVAPS

	CPAP	BiPAP	AVAPS
Settings	• Initiate PEEP at 5 cm H_2O • Increase by increments of 1-2 cm H_2O • Max 20 cm H_2O • F_{IO_2} 0.21-1	• Initiate IPAP at 10 cm H_2O and EPAP at 5 cm H_2O • Increase IPAP in increments of 2-3 cm H_2O • EPAP may also need to be increased in obese patients • Max IPAP 20-25 cm H_2O • F_{IO_2} 0.21-1	• Set goal tidal volume (6-8 mL/kgof ideal body weight) • Set EPAP at 5 cm H_2O • Set IPAP range • Minimum EPAP + 4 cm H_2O • Maximum 25 cm H_2O • F_{IO_2} 0.21-1
Benefits	• Typically best tolerated at lower pressure requirements • Simplest titration • Widely available • Well studied	• Better tolerated than CPAP at high-pressure requirements • Widely available • Well studied • Backup respiratory rate • Manipulations of IPAP/EPAP delta improve tidal volume	• Better tolerated than CPAP at high-pressure requirements • Backup respiratory rate • Tidal volume guaranteed • Better approximation of goal minute ventilation

	CPAP	BiPAP	AVAPS
Limitations	• No respiratory rate setting • No guaranteed tidal volume/minute ventilation	• No set tidal volume/minute ventilation	• Targeted but not guaranteed minute ventilation • Newer mode of NIV • Not widely available • Less well studied

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure, EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation.

Continuous positive airway pressure (CPAP) is the simplest mode of NIV. A constant pressure is set via the ventilator that is provided throughout the entire respiratory cycle. The correlate to an IMV invasive ventilator setting is the positive end–expiratory pressure (PEEP). As this mode only provides a continuous pressure, CPAP is a spontaneous mode of ventilation that requires patient initiation and respiratory muscle effort. Therefore, no respiratory rate or minute ventilation is targeted or guaranteed. **The clinical benefit of CPAP is most evident in hypoxemic respiratory failure** as the positive airway pressure predominately augments oxygenation with the goal of recruiting alveoli, increasing functional residual capacity, and decreasing shunting. CPAP is typically less uncomfortable than other NIV modes and may improve tolerance.

Bilevel positive airway pressure (BiPAP), in contrast to CPAP, provides both an expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). The EPAP setting is functionally synonymous with the CPAP mode providing a continuous baseline pressure throughout the respiratory cycle. The IPAP, however, is an additional inspiratory pressure that is either patient or ventilator triggered. The change in pressure gradient supports the muscles of respiration, resulting in an improvement in

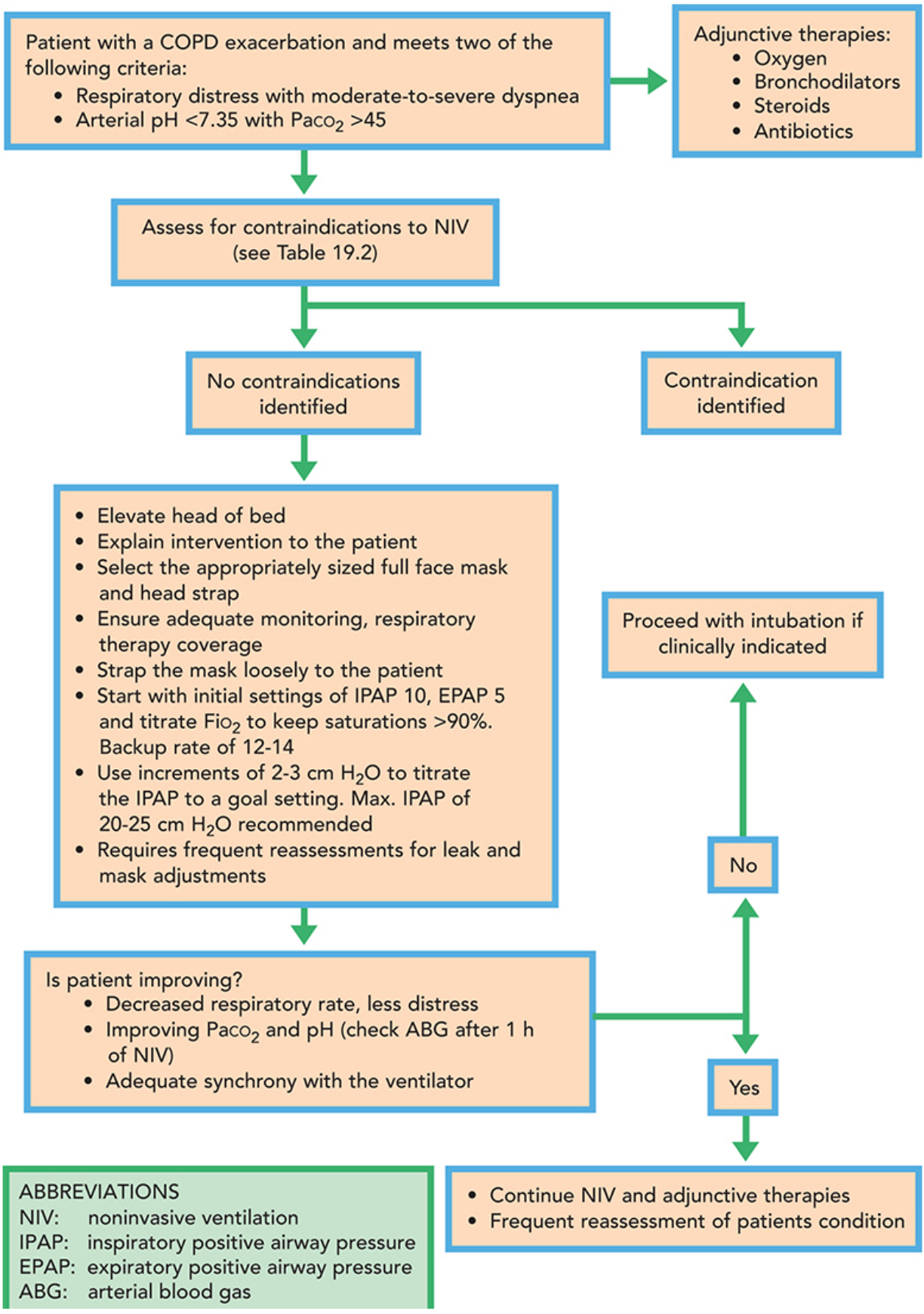
tidal volume and, thus, alveolar ventilation. As the delta between IPAP and EPAP is increased, tidal volume should also improve. Given its impact on minute ventilation and the ability to set a minimal respiratory rate, **BiPAP has utility in both hypoxemic and hypercarbic respiratory failure**.

Average volume–assured pressure support (AVAPS) is similar to BiPAP, as it provides an IPAP on continuous EPAP; the inherent difference is the clinician-defined parameters. An EPAP is identically chosen as in BiPAP; however, an IPAP range is selected to target a goal tidal volume. Therefore, as patient effort varies, the NIV will either uptitrate IPAP to increase or downtitrate to decrease to the targeted inhaled tidal volume. By setting a minimal respiratory rate and target inhaled tidal volume, a provider can more closely target a goal minute ventilation. **Thus, AVAPS also has utility in both hypoxemic and hypercarbic respiratory failure.**

SPECIFIC CLINICAL SCENARIOS

AECOPD has been the benchmark for NIV use in the intensive care unit (ICU). In these patients, NIV compared to IMV reduces the risk of hospital-acquired pneumonia, shortens length of stay, decreases cost, and improves hospital mortality. Algorithm 19.1 provides a generic algorithmic approach to initiating BiPAP in a patient with AECOPD.

ALGORITHM 19.1 **Initiation of Bilevel Positive Airway Pressure (BiPAP) in a Patient With a Chronic Obstructive Pulmonary Disease (COPD) Exacerbation**


Patient with a COPD exacerbation and meets two of the following criteria:
• Respiratory distress with moderate-to-severe dyspnea
• Arterial pH <7.35 with $Paco_2$ >45
Adjunctive therapies:
• Oxygen
• Bronchodilators
• Steroids
• Antibiotics
Assess for contraindications to NIV (see Table 19.2)
No contraindications identified
Contraindication identified
• Elevate head of bed
• Explain intervention to the patient
• Select the appropriately sized full face mask and head strap
• Ensure adequate monitoring, respiratory therapy coverage
• Strap the mask loosely to the patient
• Start with initial settings of IPAP 10, EPAP 5 and titrate Fio_2 to keep saturations >90%. Backup rate of 12-14
• Use increments of 2-3 cm H_2O to titrate the IPAP to a goal setting. Max. IPAP of 20-25 cm H_2O recommended
• Requires frequent reassessments for leak and mask adjustments
Proceed with intubation if clinically indicated
Is patient improving?
• Decreased respiratory rate, less distress
• Improving $Paco_2$ and pH (check ABG after 1 h of NIV)
• Adequate synchrony with the ventilator
No
Yes
• Continue NIV and adjunctive therapies
• Frequent reassessment of patients condition
ABBREVIATIONS
NIV: noninvasive ventilation
IPAP: inspiratory positive airway pressure
EPAP: expiratory positive airway pressure
ABG: arterial blood gas

Asthma exacerbations, although often treated with NIV, do not have strong evidence supporting its use. Extrapolating data from AECOPD would suggest a clinical benefit. As status asthmaticus is difficult to manage with IMV, a trial of NIV is reasonable while other pharmacotherapy is administered. As with any patient, intubation and IMV should proceed if no improvement.

Acute cardiopulmonary edema treated with NIV improves gas exchange and symptomatic dyspnea better than standard oxygen therapy. CPAP is a standard therapy; however, for those with underlying lung disease, worsened lung mechanics, or hypercarbia, BiPAP may be a more appropriate choice. Use of NIV in this population results in reduced intubation rates and decreased in-hospital mortality.

Studies on patients with pneumonia treated with NIV have yielded conflicting results: some showing benefit, and others demonstrating potential harm. As the pathophysiology and clinical course frequently take several days to improve, NIV may not alter the need for IMV, especially if secretions are copious and airway clearance is an issue. Practitioners should use clinical judgment while selecting these patients for an NIV trial and not hesitate to proceed to intubation if necessary. A caveat is in immunocompromised patients, supporting a different pathophysiology in the host response to pneumonia. Some trials have shown that in immunocompromised patients with acute hypoxemic respiratory failure secondary to pneumonia, NIV showed benefit with a decrease in intubation rate, ICU duration, and ICU mortality. Other studies have been unable to demonstrate similar benefits and showed NIV may actually increase mortality. Regardless, societal guidelines suggest a trial of NIV may be reasonable in immunocompromised patients with pneumonia.

NIV postextubation reduces the rate of reintubation and improves mortality. These benefits are most prominent in patients with chronic obstructive pulmonary disease (COPD); however, smaller studies have shown similar outcomes in a mixed population. NIV does not prevent reintubation when applied after a recently extubated patient

develops new respiratory failure and may in fact increase mortality in this population.

Beyond acute indications in the ICU, chronic outpatient nocturnal NIV is common in diseases such as obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and neuromuscular conditions. In this setting, benefits in sleep architecture, nocturnal oxygen, and carbon dioxide levels are evident. Patients with these comorbidities are frequently admitted to the ICU; continuation of NIV is appropriate when no contraindications exist.

Monitoring

Regardless of the interface, appropriate fit is key to assuring patient comfort and providing effective ventilatory support. Air leaks due to poorly fitting masks impair detection of inspiratory effort and end expiration. Overly tight masks can lead to pressure ulcers and skin necrosis. Careful adjustment of the ventilator settings and mask fit improves patient tolerance and compliance. Alternating mask interfaces can sometimes be employed to limit the risk of pressure ulcers. More recently, a helmet interface has been developed and approved, though its adoption remains slow and requires adequately trained staff to properly implement. Importantly, the delivered tidal volume is displayed as opposed to exhaled tidal volume as on an invasive ventilator.

Patients receiving NIV require close monitoring and frequent assessments. Most patients require admission to an intensive or respiratory care unit. Sequential assessment of mental status, respiratory rate, accessory muscle usage, chest wall movement, coordination of respiratory effort with the ventilator, and overall comfort is necessary. Periodic monitoring with arterial blood gas analysis adds objective data and evaluates response to NIV. Breaks from NIV, assuming clinically acceptable, may improve overall tolerance allowing for a longer duration if needed.

The use of NIV should never delay clinically indicated endotracheal intubation and IMV. Moreover, NIV is a supportive

therapy and patients require prompt treatment of the underlying medical conditions leading to respiratory failure.

Conclusions

NIV has become a valuable tool for the management of respiratory failure. When employed appropriately, it may negate the need for endotracheal intubation and associated complications. However, mask choice, NIV settings, and close monitoring are required to optimize success.

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SECTION III CARDIAC DISORDERS

20 Acute Myocardial Infarction

Colin Martz and Marc A. Sintek

Acute myocardial infarction (AMI) is a common diagnosis among hospitalized and critically ill patients. There are approximately 605,000 new AMIs and 200,000 recurrent AMIs diagnosed annually in the United States; three-fourths of these events will be non–ST-elevation acute coronary syndromes (NSTE-ACS). Despite improved survival during the last several decades, roughly one in five patients admitted with AMI will die within the following year.

A rapid and detailed assessment of symptoms is crucial in determining the likelihood of acute coronary syndrome (ACS) in the patient presenting with chest discomfort. Patients with ACS typically complain of moderate-to-severe chest discomfort that lasts more than 20 minutes. Atypical presentations are not uncommon in women, patients with diabetes, and the older adults. An electrocardiogram (ECG) and cardiac-specific serum biomarkers (preferably troponin I or T) are needed to distinguish between ST-segment elevation ACS (STE-ACS), NSTE-ACS, and noncardiac chest pain. It is important to differentiate *myocardial injury*, which is indicated by an abnormal troponin assay, from *myocardial infarction* (MI), which is characterized by the combination of an abnormal troponin assay with a clinical syndrome of ischemia. Indeed, MI represents a subset of myocardial injury. Several common causes of myocardial injury include heart failure, myocarditis, cardiomyopathy, Takotsubo cardiomyopathy, cardiac contusions, and defibrillator shocks. Patients who present with ACS and STE on ECG have actively infarcting myocardium and are termed *ST-elevation myocardial infarction* (STEMI) or STE-ACS. Previously, patients with ACS but without STEs were stratified as unstable angina (UA) in the absence of elevated serum cardiac biomarkers, or *non–ST-segment elevation myocardial infarction* (NSTEMI) in their presence. Recent

guidelines emphasize the continuum between UA and NSTEMI and therefore consider these entities together under the diagnosis of NSTE-ACS. The goal of the initial evaluation for the patient with ACS is prompt diagnosis of STE-ACS or NSTE-ACS with concurrent treatment of the patient's ischemia.

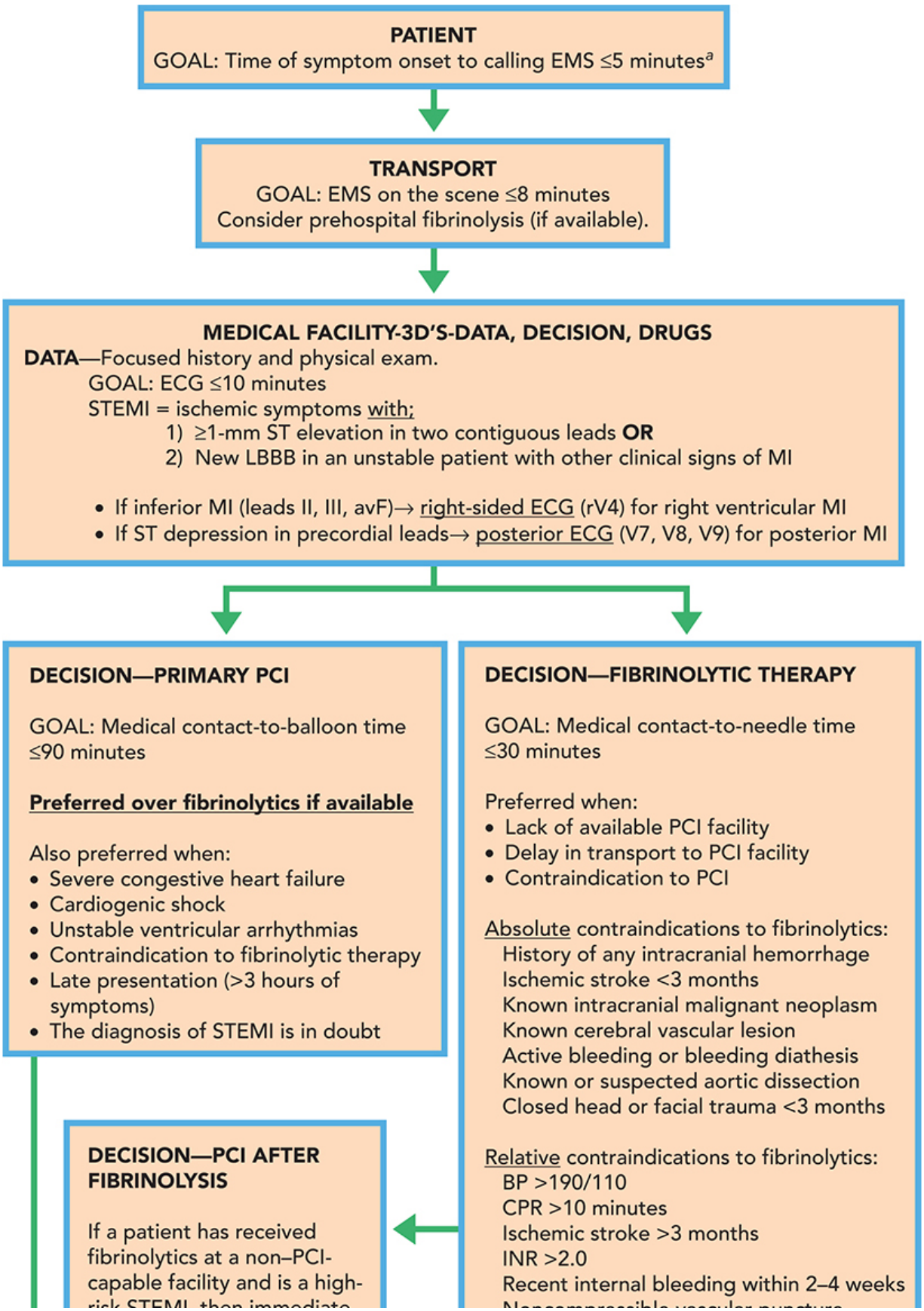
ST-Elevation Acute Coronary Syndrome

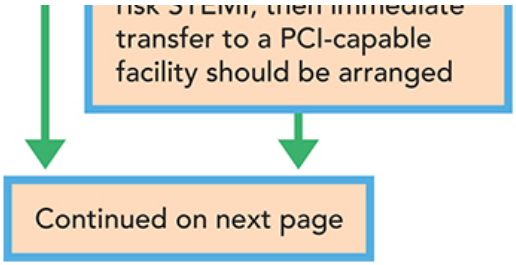
STE-ACS results from a sudden complete occlusion of a coronary artery, which is usually due to plaque rupture in an atherosclerotic coronary artery. Other causes, such as coronary embolism, can also precipitate an STE-ACS. The resultant cascade of events associated with plaque rupture involves platelet activation/aggregation and ultimately thrombus formation. Over the last few decades, 30-day mortality in STE-ACS has declined to approximately 10% to 15%. Much of the early mortality is attributable to ventricular arrhythmias. Extent of cardiac myocyte death worsens with ischemic time and correlates strongly with cardiac morbidity and mortality, leading to the oft-quoted phrase "time is muscle." As such, mechanical and medical therapies designed to reestablish blood flow in the shortest time possible are the mainstay of the therapy.

A management pathway that combines established benchmark goals and treatment options for the patient with STE-ACS/STEMI is essential for optimal care (Algorithm 20.1, Table 20.1). Mechanical support with an intra-aortic balloon pump (IABP) or a percutaneous ventricular assist device (such as Impella 2.5 or 5.0) in the patient with hemodynamic or rhythm instability, severe heart failure, or cardiogenic shock should be considered, but randomized clinical trial data demonstrating benefit to these devices are lacking (and in the case of IABP, suggest no benefit).

ALGORITHM 20.1 **Goals and Treatment of ST-Segment Elevation Myocardial Infarction/ST-**

Segment Elevation Acute Coronary Syndrome


PATIENT
GOAL: Time of symptom onset to calling EMS ≤5 minutes[a]
TRANSPORT
GOAL: EMS on the scene ≤8 minutes
Consider prehospital fibrinolysis (if available).
MEDICAL FACILITY-3D'S-DATA, DECISION, DRUGS
DATA—Focused history and physical exam.
GOAL: ECG ≤10 minutes
STEMI = ischemic symptoms with;
1) ≥1-mm ST elevation in two contiguous leads OR
2) New LBBB in an unstable patient with other clinical signs of MI
• If inferior MI (leads II, III, avF)→ right-sided ECG (rV4) for right ventricular MI
• If ST depression in precordial leads→ posterior ECG (V7, V8, V9) for posterior MI
DECISION—PRIMARY PCI
GOAL: Medical contact-to-balloon time ≤90 minutes
Preferred over fibrinolytics if available
Also preferred when:
• Severe congestive heart failure
• Cardiogenic shock
• Unstable ventricular arrhythmias
• Contraindication to fibrinolytic therapy
• Late presentation (>3 hours of symptoms)
• The diagnosis of STEMI is in doubt
DECISION—FIBRINOLYTIC THERAPY
GOAL: Medical contact-to-needle time ≤30 minutes
Preferred when:
• Lack of available PCI facility
• Delay in transport to PCI facility
• Contraindication to PCI
Absolute contraindications to fibrinolytics:
History of any intracranial hemorrhage
Ischemic stroke <3 months
Known intracranial malignant neoplasm
Known cerebral vascular lesion
Active bleeding or bleeding diathesis
Known or suspected aortic dissection
Closed head or facial trauma <3 months
Relative contraindications to fibrinolytics:
BP >190/110
CPR >10 minutes
Ischemic stroke >3 months
INR >2.0
Recent internal bleeding within 2–4 weeks
DECISION—PCI AFTER FIBRINOLYSIS
If a patient has received fibrinolytics at a non–PCI-capable facility and is a high-



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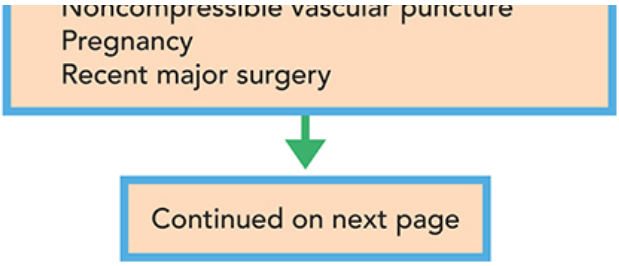

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DRUGS—Unless contraindicated, all patients receive:

- Aspirin 162–325 mg chewed
- IV nitroglycerin, started at 10 mcg/min and titrated for symptoms[c]
- Consider morphine sulfate 2–4 mg IV for chest pain unresponsive to nitrates
- Options for anticoagulant therapy in patients treated with **primary PCI**:
  - Unfractionated heparin (UFH): 50–70 U/kg IV bolus, max 4000–5000 U; then 12 U/kg/hr, max 1000 U/hr
  - Bivalirudin: 0.75 mg/kg IV bolus; then 1.75 mg/kg/hr IV infusion until PCI
- Options for anticoagulant therapy in patients treated with **fibrinolysis**:
  - Enoxaparin (Lovenox): If <75 years, 30 mg IV bolus followed by 1 mg/kg SQ Q12H (first SQ dose should be given with IV bolus, max of 100 mg for first two SQ doses); if >75 years, then omit IV bolus and inject 0.75 mg/kg SQ Q12H; avoid if Cr >2.0
  - UFH: 60–100 U/kg IV bolus, max 4000 units, then 12 U/kg/hr (max 1000 U/hr) to goal aPTT 50–70 seconds
  - Fondaparinux: 2.5 mg IV, then 2.5 mg SQ Q24H; avoid in CrCl <30 mL/min
- Options for antiplatelet therapy:
  Note: If there is a high suspicion for CAD that may require CABG (i.e., diabetes or known multivessel CAD), consider withholding a loading dose until the anatomy is defined:
  - Clopidogrel (Plavix) 300–600 mg PO loading dose
  - Ticagrelor (Brilinta) 180 mg loading dose
  - Prasugrel (Effient) 60 mg PO loading dose for patients at the time of PCI only; avoid use if body weight <60 kg, history of stroke/TIA, age ≥75 years, or increased risk of bleeding

DRUGS—PRIMARY PCI

Use of and selection of a GP-IIb/IIIa inhibitor should be determined at the time of PCI by the interventional cardiologist

REPERFUSION—PRIMARY PCI

GOAL: Restoration of TIMI 3 flow (i.e., complete perfusion)

Advantages of PCI over fibrinolytics:

1) Superior restoration of coronary flow
2) Defines anatomy
3) Fewer complications
4) Treatment of thrombus AND plaque

DRUGS—FIBRINOLYTIC

Regimens include:

Alteplase + UFH

Alteplase 15 mg bolus, then 0.75 mg/kg (max 50 mg) over 30 minutes, then 0.5 mg/kg (max 35 mg) over next 60 minutes

UFH IV as detailed above

Reteplase (Retavase) + UFH

Reteplase 10 U IV bolus over 2 minutes and repeat 10 U IV bolus 30 minutes later

UFH IV as detailed above

Tenecteplase (TNKase) + UFH

TNKase dose is based on weight (see **Table 19.1**)

UFH IV as detailed above

REPERFUSION—THROMBOLYSIS

Considered successful if:

1) Complete resolution of chest pain
2) ST-segment elevation improvement >50%

If unsuccessful or the development of hemodynamic or electrical instability, consider transfer to center capable of rescue PCI

ABBREVIATIONS

aPPT: activated partial thromboplastin time
BP: blood pressure
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CPR: cardiopulmonary resuscitation
Cr: creatinine
ECG: electrocardiogram
EMS: emergency medical services
GP: glycoprotein
INR: international normalized ratio
IV: intravenous
LBBB: left bundle branch block

MI:	myocardial infarction
PCI:	percutaneous coronary intervention
PO:	by mouth
Q12H:	every 12 hours
Q2H4:	every 24 hours
SQ:	subcutaneous
STEMI:	ST-elevation myocardial infarction
TIA:	transient ischemic attack
TIMI:	thrombolysis in myocardial infarction
UFH:	unfractionated heparin

[a]Patients who have taken SL nitroglycerin should call 911 if symptoms do not improve or worsen within 5 minutes of taking one SL nitroglycerin.

[b]Caution if suspected inferior MI, SBP <90 mm Hg, HR <50 bpm or >100 bpm, or phosphodiesterase inhibitors for erectile dysfunction in past 24 to 48 hours.

TABLE 20.1 TNKase Dosing

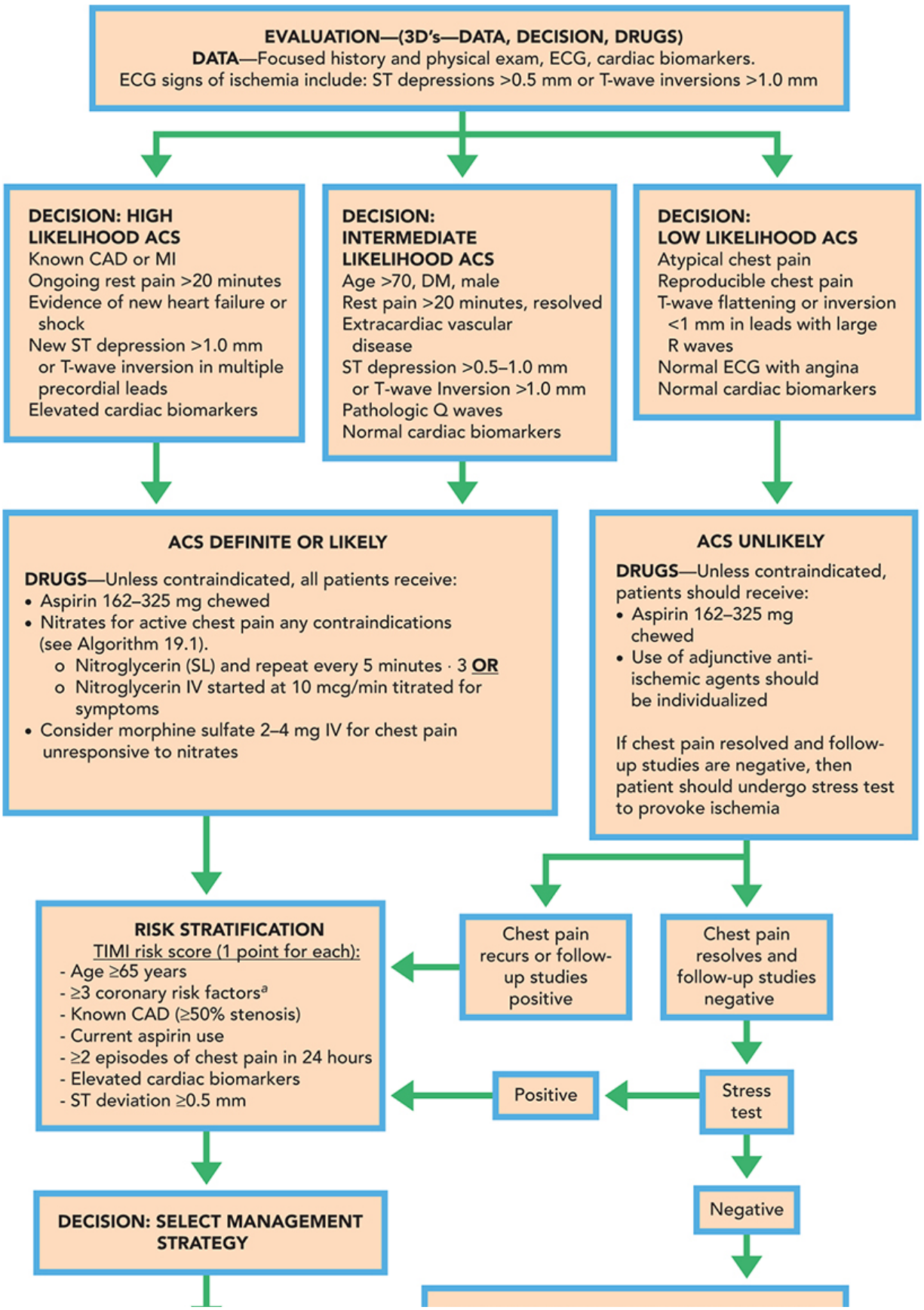
Weight (kg)	TNKase (mg)
<60	30
60-69	35
70-79	40
80-89	45
≥90	50

Non–ST Elevation Acute Coronary Syndrome

The evaluation and management of patients with NSTE-ACS is outlined in Algorithm 20.2. Patients who present with NSTE-ACS should undergo evaluation to assess for risk of major adverse cardiac events (MACE), defined as death, nonfatal MI, and stroke. A useful and well-validated method for risk stratification is the Thrombolysis in Myocardial Infarction (TIMI) risk score. Patients with a higher score are more likely to suffer from MACE than those with a

lower score. All patients should receive medical management appropriate to their level of risk and, importantly, should be considered for diagnostic angiography with intent to perform percutaneous coronary intervention (PCI). High-risk patients benefit from early revascularization therapies, as do patients with hemodynamic instability, electrical instability (ie, ventricular arrhythmias), and chest pain refractory to high-dose nitroglycerin infusion.

ALGORITHM 20.2 Risk Stratification and Treatment for Non–ST-Segment Elevation Myocardial Infarction


EVALUATION—(3D's—DATA, DECISION, DRUGS)
DATA—Focused history and physical exam, ECG, cardiac biomarkers.
ECG signs of ischemia include: ST depressions >0.5 mm or T-wave inversions >1.0 mm
DECISION: HIGH LIKELIHOOD ACS
Known CAD or MI
Ongoing rest pain >20 minutes
Evidence of new heart failure or shock
New ST depression >1.0 mm or T-wave inversion in multiple precordial leads
Elevated cardiac biomarkers
DECISION: INTERMEDIATE LIKELIHOOD ACS
Age >70, DM, male
Rest pain >20 minutes, resolved
Extracardiac vascular disease
ST depression >0.5–1.0 mm or T-wave Inversion >1.0 mm
Pathologic Q waves
Normal cardiac biomarkers
DECISION: LOW LIKELIHOOD ACS
Atypical chest pain
Reproducible chest pain
T-wave flattening or inversion <1 mm in leads with large R waves
Normal ECG with angina
Normal cardiac biomarkers
ACS DEFINITE OR LIKELY
DRUGS—Unless contraindicated, all patients receive:
• Aspirin 162–325 mg chewed
• Nitrates for active chest pain any contraindications (see Algorithm 19.1).
o Nitroglycerin (SL) and repeat every 5 minutes · 3 OR
o Nitroglycerin IV started at 10 mcg/min titrated for symptoms
• Consider morphine sulfate 2–4 mg IV for chest pain unresponsive to nitrates
ACS UNLIKELY
DRUGS—Unless contraindicated, patients should receive:
• Aspirin 162–325 mg chewed
• Use of adjunctive anti-ischemic agents should be individualized
If chest pain resolved and follow-up studies are negative, then patient should undergo stress test to provoke ischemia
RISK STRATIFICATION
TIMI risk score (1 point for each):
- Age ≥65 years
- ≥3 coronary risk factors[a]
- Known CAD (≥50% stenosis)
- Current aspirin use
- ≥2 episodes of chest pain in 24 hours
- Elevated cardiac biomarkers
- ST deviation ≥0.5 mm
Chest pain recurs or follow-up studies positive
Chest pain resolves and follow-up studies negative
Positive
Stress test
Negative
DECISION: SELECT MANAGEMENT STRATEGY

Continued on next page

Diagnosis: Likely noncardiac chest discomfort

Arrange for outpatient follow-up

Discharge medications based on risk factors for cardiovascular disease

DECISION: SELECT MANAGEMENT STRATEGY

Favors Invasive Strategy:
Recurrent chest pain despite maximal medical therapy
Elevated cardiac biomarkers
New ST-segment depression
Signs of heart failure
New or worsening mitral regurgitation
Hemodynamic instability
Sustained ventricular tachycardia
Prior CABG
High-risk score (e.g., TIMI 5–7)
PCI within 6 months
Reduced LV ejection fraction

Favors Conservative Strategy:
Low-risk score (e.g., TIMI 0–2)
Patient or physician preference
Risk of revascularization outweighs benefits

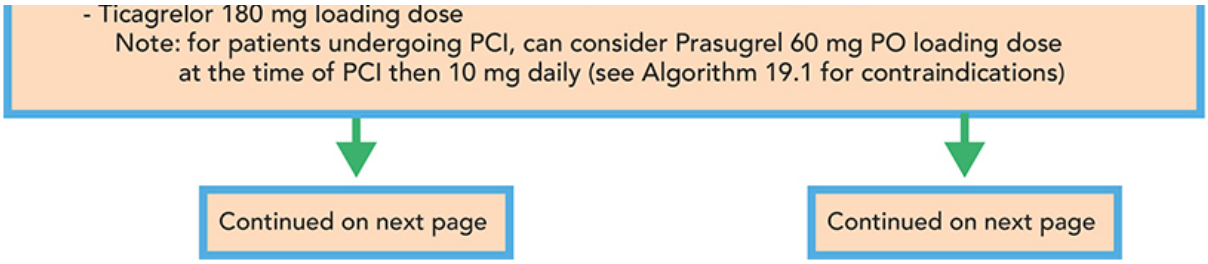
Calculated TIMI Score	14-day Risk of MACE
0 or 1	5%
2	8%
3	13%
4	20%
5	26%
6 or 7	41%

INVASIVE STRATEGY
(i.e., Diagnostic catheterization with intent to perform PCI)

Early invasive strategy (i.e., requiring immediate catheterization) should be considered in patients with:
- Refractory chest discomfort despite vigorous medical therapy
- Hemodynamic or rhythm instability

CONSERVATIVE STRATEGY

DRUGS—Unless contraindicated, all patients should receive the following regardless of the strategy:
- Options for anticoagulant therapy:
  - Unfractionated heparin, **preferred in early invasive approach**: 60–70 U/kg IV bolus, max 4000–5000 U; then 12 U/kg/hr (max 1000 U/hr), adjusted to achievegoal aPTT of 50–70 seconds
  - Bivalirudin (Angiomax), **preferred in early invasive approach**: 0.1 mg/kg IV bolus; then 0.25 mg/kg/hr until angiography performed
  - Enoxaparin (Lovenox), **preferred in noninvasive strategy**: If NSTE-ACS and not undergoing early invasive approach, no loading dose necessary. Dosing is 1 mg/kg SQ q12h. If CrCl <30 mL/min, dose is 1 mg/kg q24h
  - Fondaparinux (Arixtra), **preferred in noninvasive strategy**: 2.5 mg SQ q24h, avoid if CrCl <30 mL/min
- Options for dual antiplatelet therapy:
  For the invasive strategy, if there is a high suspicion for CAD that may require CABG (e.g., diabetes or known multivessel CAD), then consider with holding therapy and starting a GP IIb/IIIa inhibitor until the anatomy is defined:
  - Clopidogrel (Plavix) 300–600 mg PO loading dose then 75 mg daily


- Ticagrelor 180 mg loading dose
Note: for patients undergoing PCI, can consider Prasugrel 60 mg PO loading dose at the time of PCI then 10 mg daily (see Algorithm 19.1 for contraindications)
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INVASIVE STRATEGY
(i.e., diagnostic catheterization with intent to perform PCI)

Addition of a GP IIb/IIIA inhibitor (generally at time of PCI) can be considered in patients who have not received bivalirudin and who:

- Have refractory chest discomfort despite vigorous medical therapy
- Are high risk with positive troponins
- Have a delay to angiography >48 hours

Eptifibatide (Integrilin): 180 µg/kg bolus (max 22.6 mg), then 2 mcg/kg/min (max 15 mg/hr) infusion. Requires dose adjustment if CrCl <50 mL/min

OR

Tirofiban (Aggrastat): 25 mcg/kg loading dose, then 0.15 mcg/kg/min maintenance infusion for up to 18 hours. Requires dose adjustment if CrCl <60 mL/min

ABBREVIATIONS

AAA:	abdominal aortic aneurysm
ACS:	acute coronary syndrome
aPPT:	activated partial thromboplastin time
AS:	aortic stenosis
BPM:	beats per minute
CABG:	coronary artery bypass grafting
CAD:	coronary artery disease
CP:	chest pain
CrCl:	creatinine clearance
CVA:	cerebrovascular accident
DM:	diabetes mellitus
ECG:	electrocardiogram
EF:	ejection fraction
GP:	glycoprotein
HR:	heart rate
HTN:	hypertension
IV:	intravenous
LVEF:	left ventricular ejection fraction
MACE:	major adverse cardiac events
MI:	myocardial infarction
NSTE:	non-ST elevation
PAD:	peripheral arterial disease
PCI:	percutaneous coronary intervention
PO:	by mouth
Q12H:	every 12 hours
Q2H4:	every 24 hours
SBP:	systolic blood pressure
SL:	sublinqual
SQ:	subcutaneous
TIMI:	thrombolysis in myocardial infarction

CONSERVATIVE STRATEGY

Any events necessitating catheterization?

- Hemodynamic instability
- Rhythm instability
- Recurrent symptoms despite medical therapy
- Heart failure

YES

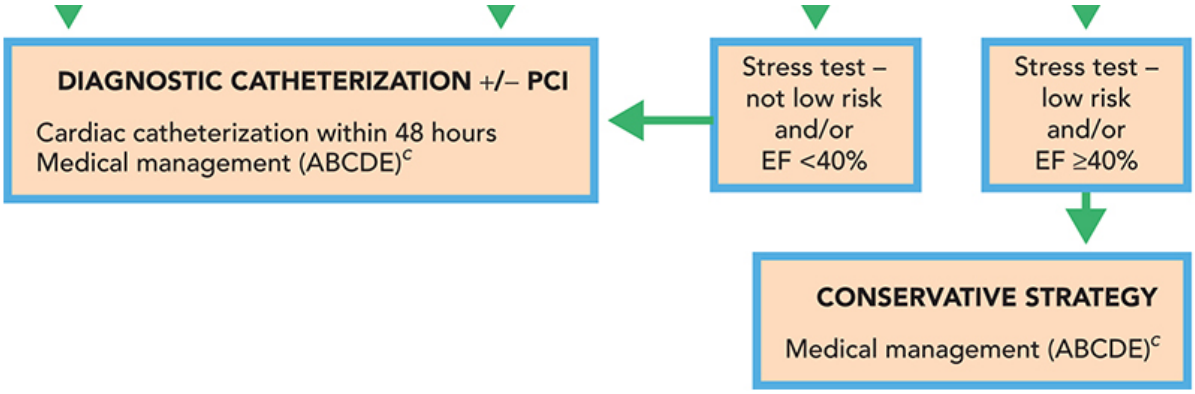
NO

CONSERVATIVE STRATEGY

Noninvasive cardiac stress test[b]
Exercise is preferred for prognostic information
Avoid adenosine if bronchospasm
Avoid dobutamine if tachyarrhythmias, severe AS, uncontrolled HTN, AAA.

AND/OR

Evaluate LVEF


DIAGNOSTIC CATHETERIZATION +/– PCI
Cardiac catheterization within 48 hours
Medical management (ABCDE)c
Stress test – not low risk and/or EF <40%
Stress test – low risk and/or EF ≥40%
CONSERVATIVE STRATEGY
Medical management (ABCDE)c

[a]Coronary risk factors include diabetes mellitus, cigarette smoking, hypertension (>140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature coronary artery disease (CAD) (male first-degree relative ≤55 years old or female first-degree relative ≤65 years old), and age (men ≥45 years old; women ≥55 years old).

[b]Diagnostic accuracy of various stress tests is as follows: exercise treadmill: men—68% sensitive, 77% specific, women—61% sensitive, 70% specific; exercise, adenosine thallium—88% sensitive, 77% specific; Exercise or dobutamine echo—76% sensitive, 88% specific.

[c]See Table 20.2.

Hospital Care of the Patient With Acute Coronary Syndrome

Patients with ACS are at an increased risk for recurrent MI and death during both hospitalization and after discharge. Hospitalization and subsequent office visits provide venues with which to work with patients to reduce the risk of further events. The mnemonic “ABCDE” helps to organize the various in-hospital and postdischarge treatments (Table 20.2). These items can be considered an acute treatment guide as well as a discharge checklist for any patient admitted with ACS. The management of suspected MI in the setting of cardiac arrest is discussed further in Chapter 25, Post Cardiac Arrest Management.

TABLE 20.2 ABCDEs as an Inpatient Treatment Guide and Discharge Checklist for Patients With Acute Coronary Syndrome

A	Antiplatelet	Aspirin indefinitely Clopidogrel (or other antiplatelet agent) for at least 1 y Consider PPI prophylaxis in patients with risk factors for or history of PUD/GI bleeding
	Anticoagulation	Heparin or enoxaparin during hospitalization
	ACE inhibitor (ACE-I)	Consider if EF (≤40%), DM, CRI, or HTN
	Angiotensin receptor blocker	For ACE-I intolerant patients
	Aldosterone receptor blocker	For patients with EF <40% with DM or HF who are already on an ACE-I and beta-blocker; caution in patients with hyperkalemia or CRI
B	Beta-blocker	All patients unless contraindicated
	Blood pressure	Goal <140/90 mm Hg; for CRI or DM, the goal is <130/80 mm Hg (maximize therapy with beta-blocker and ACE-I before adding additional anti-HTN medications)
C	Cigarette cessation	Complete cessation. Nicotine replacement, oral medications, counseling
	Cholesterol	High-intensity statin therapy regardless of LDL
D	Diet	If BMI >25, the initial goal is to reduce weight by 10%.
	Diabetes	Goal HbA_{1c} <7.0%
E	Exercise	30 min of aerobic activity a minimum of 5 d/wk Referral for cardiac rehabilitation
	Ejection	Measurement of ejection fraction prior to discharge

fraction

ACE, angiotensin-converting enzyme; BMI, body mass index; CRI, chronic renal insufficiency; DM, diabetes mellitus; EF, ejection fraction; GI, gastrointestinal; HF, heart failure; Hb, hemoglobin; HTN, hypertension; LDL, low-density lipoprotein; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

CLASSIFYING MYOCARDIAL INFARCTIONS

Classification of different types of MIs is important as their management may differ from the recommendations for STE and NSTE-ACS (Table 20.3). A type 1 MI is due to ischemia from an unstable coronary plaque and leads to thrombus formation, which may (as in STE-ACS) or may not (as in NSTE-ACS) completely occlude blood flow. A type 2 MI occurs with an *increased demand* or a *decreased supply* of myocardial oxygen. Typically, patients with type 2 MIs have fixed coronary artery stenoses that do not cause ischemia at rest but can induce ischemia at times of increased oxygen utilization (eg, tachycardia, surgery, and severe hypertension) or decreased oxygen delivery (eg, anemia, hypoxia, hypotension, and sepsis). Intraoperative MIs are most commonly due to myocardial oxygen supply-demand mismatch and often manifest postoperatively as elevated cardiac biomarkers. Our recommended algorithm for the treatment of type 2 MI is shown in Algorithm 20.3.

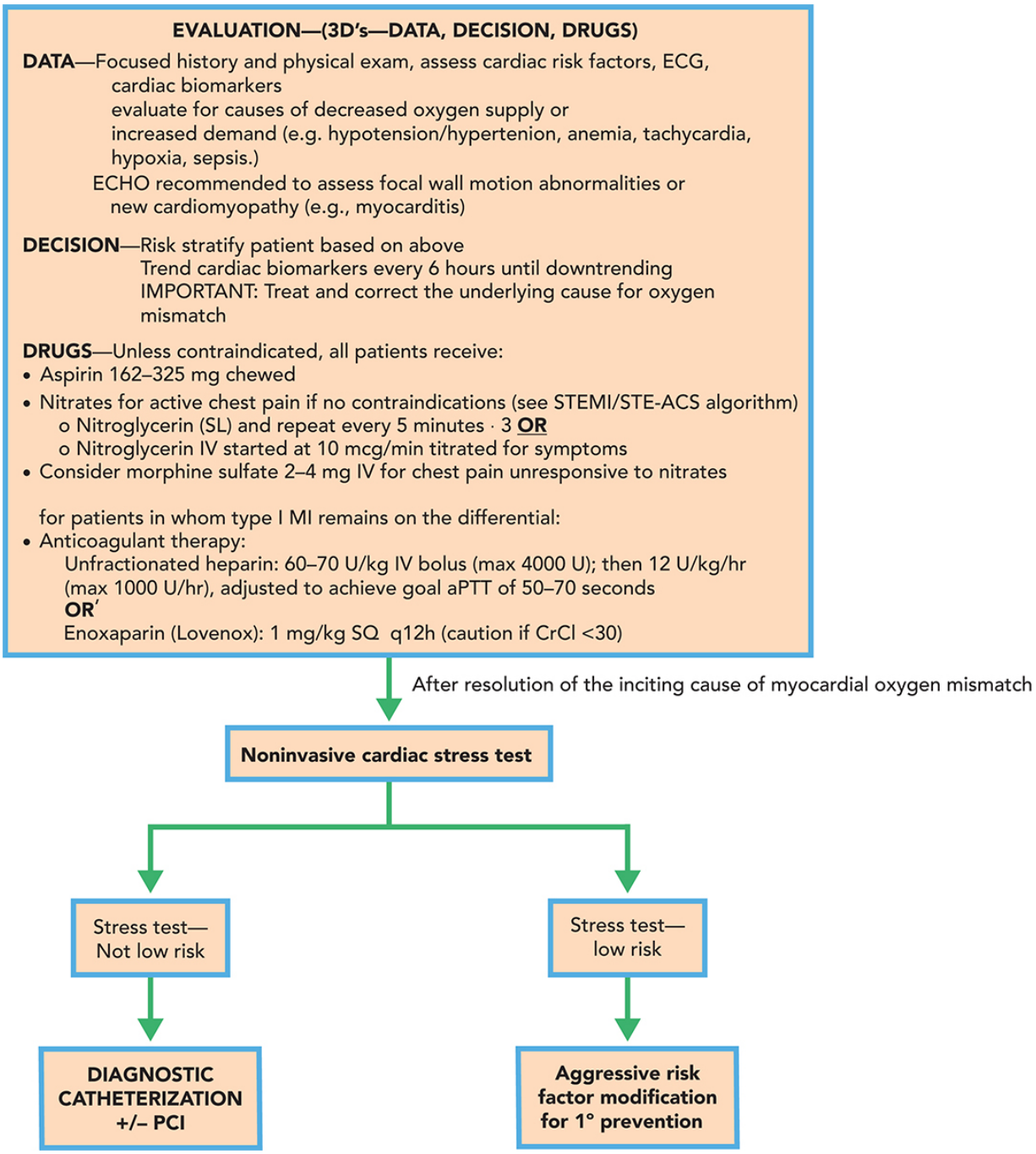
TABLE 20.3 Classification of Different Types of Myocardial Infarction

	Clinical Scenario
Type 1	Spontaneous MI secondary to a primary coronary event due to plaque instability
Type 2	MI secondary to myocardial oxygen supply-demand mismatch
Type 3	Sudden cardiac death

	Clinical Scenario
Type 4a	MI secondary to PCI (Note: cTn values must be >5 × 99th percentile URL)
Type 4b	MI secondary to stent thrombosis
Type 5	MI associated with CABG (Note: cTn values must be >10 × 99th percentile URL)

CABG, coronary artery bypass grafting; cTn, cardiac troponin; MI, myocardial infarction; PCI, percutaneous coronary intervention; URL, upper reference limit.

ALGORITHM 20.3 Management Algorithm for Type 2 Myocardial Infarction


EVALUATION—(3D's—DATA, DECISION, DRUGS)
DATA—Focused history and physical exam, assess cardiac risk factors, ECG, cardiac biomarkers
evaluate for causes of decreased oxygen supply or increased demand (e.g. hypotension/hypertenion, anemia, tachycardia, hypoxia, sepsis.)
ECHO recommended to assess focal wall motion abnormalities or new cardiomyopathy (e.g., myocarditis)
DECISION—Risk stratify patient based on above
Trend cardiac biomarkers every 6 hours until downtrending
IMPORTANT: Treat and correct the underlying cause for oxygen mismatch
DRUGS—Unless contraindicated, all patients receive:
• Aspirin 162–325 mg chewed
• Nitrates for active chest pain if no contraindications (see STEMI/STE-ACS algorithm)
o Nitroglycerin (SL) and repeat every 5 minutes · 3 OR
o Nitroglycerin IV started at 10 mcg/min titrated for symptoms
• Consider morphine sulfate 2–4 mg IV for chest pain unresponsive to nitrates
for patients in whom type I MI remains on the differential:
• Anticoagulant therapy:
Unfractionated heparin: 60–70 U/kg IV bolus (max 4000 U); then 12 U/kg/hr (max 1000 U/hr), adjusted to achieve goal aPTT of 50–70 seconds
OR'
Enoxaparin (Lovenox): 1 mg/kg SQ q12h (caution if CrCl <30)
After resolution of the inciting cause of myocardial oxygen mismatch
Noninvasive cardiac stress test
Stress test—Not low risk
Stress test—low risk
DIAGNOSTIC CATHETERIZATION +/– PCI
Aggressive risk factor modification for 1° prevention

Two unique forms of myocardial injury are stress-induced ("Takotsubo") and sepsis-induced cardiomyopathies. Both syndromes are driven by an excess of catecholamines and can be difficult to differentiate from ACS. Patients with these syndromes manifest ischemic ECG changes, echocardiographic abnormalities including focal wall motion abnormalities and depressed left

ventricular (LV) systolic function, and elevated cardiac biomarkers. Patients with suspected stress-induced cardiomyopathy should undergo an evaluation of the coronary arteries, though increasingly noninvasive imaging techniques (such as CT coronary angiography) may obviate cardiac catheterization. This may be normal or show only mild coronary artery disease (CAD). They should, likewise, undergo evaluation by transthoracic echocardiogram (TTE) or cardiac MRI to evaluate for possible LV dysfunction and LV outflow tract obstruction. Management includes adrenergic-blocking agent (ie, nonselective beta-blockers with alpha-blocking activity), afterload reduction with angiotensin converting enzyme (ACE) inhibitors, diuretics as needed, and serial TTEs to monitor for persistence of ventricular dysfunction. Patients with a severely depressed LV ejection fraction (LVEF) or LV thrombus should be considered for short-term oral anticoagulation. The majority of patients who overcome the inciting event or medical illness will fully recover.

Complications After Myocardial Infarction

Postinfarction complication rates have fallen dramatically since the advent of early reperfusion strategies. Nevertheless, many patients, including those with large infarction, silent infarction, late presentation, and delayed or incomplete reperfusion, remain at high risk for complications. The mnemonic FEAR AMI is a helpful way to remember these potential life-threatening complications. The following sections discuss the individual letters of this mnemonic.

FAILURE

LV dysfunction is the most powerful predictor of survival following MI. Clinical symptoms of LV dysfunction range from mild heart failure (eg, rales or S3) to cardiogenic shock. The severity of LV dysfunction correlates with the size of the infarct, advanced age, and other clinical risk factors such as diabetes. Treatment for post-MI LV dysfunction is determined by its severity and includes supplemental

oxygen, afterload reduction with vasodilators (eg, nitroglycerin or nitroprusside) and inhibition of the renin-angiotensin system, and diuretic therapy. Patients who develop cardiogenic shock warrant insertion of a pulmonary artery catheter (PAC) and may require beta-agonists (eg, dobutamine), a phosphodiesterase inhibitor (eg, milrinone), and/or vasopressor therapy. Patients with deep cardiogenic shock refractory to inotropes and vasopressors should be evaluated early for temporary mechanical **circulatory** support (tMCS) with Impella devices or veno-arterial extracorporeal membrane oxygenation (ECMO).

Right ventricular (RV) dysfunction occurs in about 10% of patients with inferior or posterior MIs. It should be suspected in those patients who develop hypotension with standard medical therapy for MI and who have an elevated jugular venous pulse in the absence of pulmonary edema. In these patients, PAC will reveal a high central venous pressure and low pulmonary capillary wedge pressure (PCWP). Management includes judicious intravenous fluids for preload and the use of dobutamine to maintain adequate cardiac output. RV support with tMCS can be pursued in select circumstances but as in the case of LV support, it has not been rigorously proven to improve outcomes in MI-CS.

EMBOLISM AND EFFUSIONS/PERICARDITIS

Up to 20% of all patients and 60% of patients suffering a large anterior wall MI will develop a mural thrombus. Contrast echocardiography should be performed in all patients with an MI to determine the presence of either a mural thrombus or akinetic segments that predispose to thrombus formation. If found, these should prompt a discussion between provider and patient regarding the risk of embolization versus the risk of bleeding with anticoagulation therapy. This is of particular concern when anticoagulation is in addition to aspirin and a $P2Y_{12}$ receptor inhibitor after PCI. If anticoagulation is desired, systemic heparin followed by approximately 3 to 6 months of oral anticoagulant therapy can be initiated.

Post-MI pericardial effusions are rarely life threatening. However, when tamponade physiology is present in a post-MI patient, a hemorrhagic effusion from a ventricular rupture must be considered. In the presence of an effusion on echocardiogram, anticoagulation should be withheld in the post-MI period to avoid possible hemopericardium. If anticoagulation cannot be stopped, heightened vigilance for this complication is warranted.

Post-MI pericarditis can present at any point from the first days after MI up to 6 weeks following infarct. This complication is due to local pericardial irritation, usually by a transmural infarct. Pericarditis must be distinguished from recurrent ischemia. Pain secondary to pericarditis is classically worse with deep inspiration, improves with sitting forward, radiates to the scapulae, and can be associated with characteristic ECG findings. This is generally self-limited and therefore managed expectantly; in rare cases with severe pain despite acetaminophen, treatment with high-dose aspirin 650 mg every 8 hours can be considered.

Dressler syndrome is a type of postinfarction pericarditis that occurs 1 to 8 weeks after the infarct. It is thought to be immune mediated and is best treated with high-dose aspirin. Glucocorticoids and other nonsteroidal anti-inflammatory agents are avoided in the first month after infarction because of the potential to impair ventricular healing and increase rates of ventricular rupture.

ARRHYTHMIA

The management of many common arrhythmias is discussed elsewhere (see Chapter 21,Cardiac Arrhythmias and Conduction Abnormalities). Several infarction-specific arrhythmias are presented here.

Various ventricular arrhythmias have been previously associated with infarction and subsequent reperfusion. The best evidence for a “reperfusion rhythm” is accelerated idioventricular rhythm (AIVR), as it is often seen immediately following successful reperfusion. Despite this, AIVR is neither very sensitive nor specific for a successful reperfusion and, if seen in the setting of reperfusion, does not

require any specific intervention. More common ECG changes following successful reperfusion involve ST-T changes such as resolution of prior ST elevation.

Ventricular tachycardia (VT) is often the terminal rhythm in the peri-infarct period and is associated with increased mortality when occurring in the first 48 hours of hospitalization. VT can be stratified into *monomorphic* VT, in which all ventricular beats have a similar morphology as is seen when the VT originates from a single focus or circuit, and *polymorphic* VT, which has a changing morphology in its ventricular beats. In each case, aggressive restoration of sinus rhythm is achieved through the use of antiarrhythmic medications (eg, amiodarone, lidocaine) and/or synchronized direct current cardioversion as per Advanced Cardiac Life Support (ACLS) guidelines. Because hypokalemia and hypomagnesemia have been associated with the development of sustained VT, it is important to correct potassium (K) and magnesium (Mg) levels in the setting of an infarction (K > 4 mEq/L and Mg > 2 mEq/L). In contrast, nonsustained VT (NSVT) is not associated with an increased risk of death during the index hospitalization or during the first year after infarction, and suppressive treatment of asymptomatic NSVT is not routinely recommended in the post-MI patient.

Infarction can cause block at any level of the conduction system. The location of the infarct has an important influence on the patient's prognosis and treatment of conduction disease. In general, right coronary artery infarct is associated with proximal (atrioventricular [AV] nodal) conduction disease. This AV block is usually transient and, in the absence of symptoms, typically does not warrant transvenous pacemaker placement. One exception is symptomatic AV block in the setting of RV infarction, as restoration of AV synchrony can improve RV filling and thus cardiac output. Left anterior descending/septal infarct is associated with distal (infranodal) conduction disease and is potentially life threatening. In general, management involves restoration of coronary perfusion rather than temporary ventricular pacing. Additional features of AV conduction disease are shown in Table 20.4. Acute treatment is discussed in Chapter 21.

TABLE 20.4 Features of Ischemia-Related Atrioventricular (AV) Conduction Disease

	Proximal Conduction Disease	Distal Conduction Disease
Compromised artery	Right coronary/posterior descending (90%)	Septal perforators of the left anterior descending
Site of block	Intranodal	Infranodal
Site of infarction	Inferoposterior	Anteroseptal
Type of AV block	First degree or Mobitz I	Mobitz II or third degree
Duration of AV block	Generally transient (2-3 d)	Variable
Mortality rate	Low, unless CHF or hypotension	High, because of extensive infarct
Temporary pacemaker	Rare	Early consideration, especially for anterior infarct and bifascicular block
Permanent pacemaker	Almost never	Indicated if high-grade block in His-Purkinje system or associated bundle branch block

CHF, congestive heart failure.

RUPTURE AND REGURGITATION

The clinical presentation of a ventricular rupture is often striking and usually life threatening. The rupture can be in the ventricular free wall, ventricular septum, or papillary muscle (Table 20.5).

TABLE 20.5 Clinical Profile of Mechanical Complications of Myocardial Infarction

	Ventricular Septal Defect	Free Wall Rupture	Papillary Muscle Rupture
Days post-MI	1-5	1-7	3-5
Anterior MI	66%	50%	25%
New murmur	90%	25%	50%
Palpable thrill	Yes	No	Rare
2D Echo findings	Visualize defect	May have pericardial effusion	Flail or prolapsing leaflet
Doppler Echo findings	Detect shunt		Regurgitant jet in LA
PA catheterization	Oxygen step-up in RV	Equalization of diastolic pressure	Prominent *c-v* wave in PCW tracing
Medical mortality	90%	90%	90%
Surgical mortality	50%	Case reports	40%-90%

LA, left atrium; MI, myocardial infarction; PA, pulmonary artery; PCW, pulmonary capillary wedge; RV, right ventricle.
Modified from Labovitz AJ. Mechanical complications of acute myocardial infarction. *Cardiovasc Rev Rep.* 1984;5:948.

Ventricular free wall rupture presents with hypotension and signs of cardiac tamponade. Any clinical suspicion warrants immediate use of echocardiography as well as PAC for prompt diagnosis. Emergent surgery is usually the only chance for survival.

Ventricular septal rupture (VSR) should be suspected in patients with a new pansystolic murmur or palpable thrill with signs of

worsening biventricular failure. Echocardiography is needed to detect and localize the VSR. PAC is useful to assess for an increase in the oxygen saturation in the right ventricle ("step-up"), which is characteristic of a VSR. PAC can also be used to calculate a shunt fraction. All patients with a VSR should be considered for early surgical therapy. IABP and/or the use of nitroprusside can be used to bridge patients to surgery by reducing the shunt.

Mitral regurgitation (MR) is a common complication of MI and is often caused by left circumflex infarction. Ischemic MR may be caused by mitral annular dilatation in LV dysfunction, papillary muscle dysfunction, or papillary muscle rupture. Typically, MR is transient and asymptomatic and does not warrant further intervention. However, MR secondary to papillary muscle rupture may be severe and should be suspected in patients with a new pansystolic murmur in the setting of heart failure, hemodynamic compromise, and pulmonary edema. Notably, some patients with severe MR in this setting may not have a prominent murmur. Echocardiography (TTE and transesophageal echocardiogram [TEE]) is essential to the diagnosis and determining the etiology of MR. PAC reveals large V waves on the PCWP tracing. For patients with suspected papillary muscle rupture, immediate surgery is indicated with the use of nitroprusside or IABP in the setting of hypotension to stabilize the patient until surgery.

ANEURYSM

True LV aneurysms complicate <5% of acute infarctions. They are thought to be a consequence of a complete occlusion of the supplying coronary artery without significant collateral blood flow. As such, anteroapical aneurysms (due to left anterior descending artery occlusion) are 4 times more common than inferoposterior aneurysms.

LV aneurysms are associated with a 6-fold increase in mortality, mainly resulting from ventricular arrhythmias. LV aneurysms are often supported by fibrous tissue and thus rarely rupture. The characteristic ECG findings of LV aneurysms are Q waves with

persistent ST elevations, although the diagnosis is best made by TTE or, if necessary, MRI. Because of the risk of mural thrombus formation and systemic embolization, patients with an LV aneurysm are often treated with long-term anticoagulation, particularly if there is evidence of significant LV dysfunction or suspected thrombus. Additionally, as ST segments may remain elevated for some time after successful reperfusion, persistent ST elevations (>4 weeks after AMI) are generally required for the ECG diagnosis of LV aneurysm. Chronic aneurysms lead to heart failure or arrhythmias. For patients with refractory symptoms, surgery may be considered to repair a chronic aneurysm.

Distinct from an aneurysm is a pseudoaneurysm. Rather than involving layers of muscle, the myocardium perforates, allowing this clinical entity to be thought of as a “contained rupture.” It is most often seen with inferior infarctions, and treatment of choice is surgery. Both surgical and medical treatments carry a very high mortality due to the risk for spontaneous rupture.

RECURRENT MYOCARDIAL INFARCTION

The complaint of chest pain after an MI may represent recurrent ischemia from incomplete revascularization, infarct extension, reinfarction, distal embolization of plaque, or postinfarction angina. Ischemia recurs in 20% to 30% of patients receiving thrombolytic therapy and up to 10% of patients after percutaneous revascularization. Serial cardiac biomarkers and ECGs can help identify at-risk patients. Troponins may not be useful, given their persistent elevation beyond 1 week after an MI. Increases in creatine kinase myocardial band (CK-MB) isoenzymes after downtrending may be a more diagnostic marker of reinfarction. Aggressive medical therapy with anti-ischemic medications (eg, aspirin, heparin, nitrates, and beta-blockers) is important to control symptoms. Revascularization should be considered in patients whose symptoms are refractory to medical therapy.

New postinfarct ST elevations can be caused by reinfarction, pericarditis, or dyskinetic/aneurysmal ventricular segments.

Reinfarction due to stent thrombosis usually has a dramatic presentation with severe anginal pain refractory to medical therapy and evolving ST elevations on ECG. These findings warrant immediate revascularization efforts.

SUGGESTED READINGS

Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation.* 2014;130(25):e344-e426.

Equally invaluable consensus guidelines for patients with NSTE-ACS.

Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284(7):835-842.

One of several validations of the popular TIMI risk score for NSTE-ACS.

Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation.* 2008;118(4):397-409.

Nice review on various types of stress-induced cardiomyopathies including their mechanism, diagnosis, and suggested management.

O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation.* 2013;127(4):e362-e425.

Invaluable consensus guidelines detailing the state of the art for management of patients with STEMI.

Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.

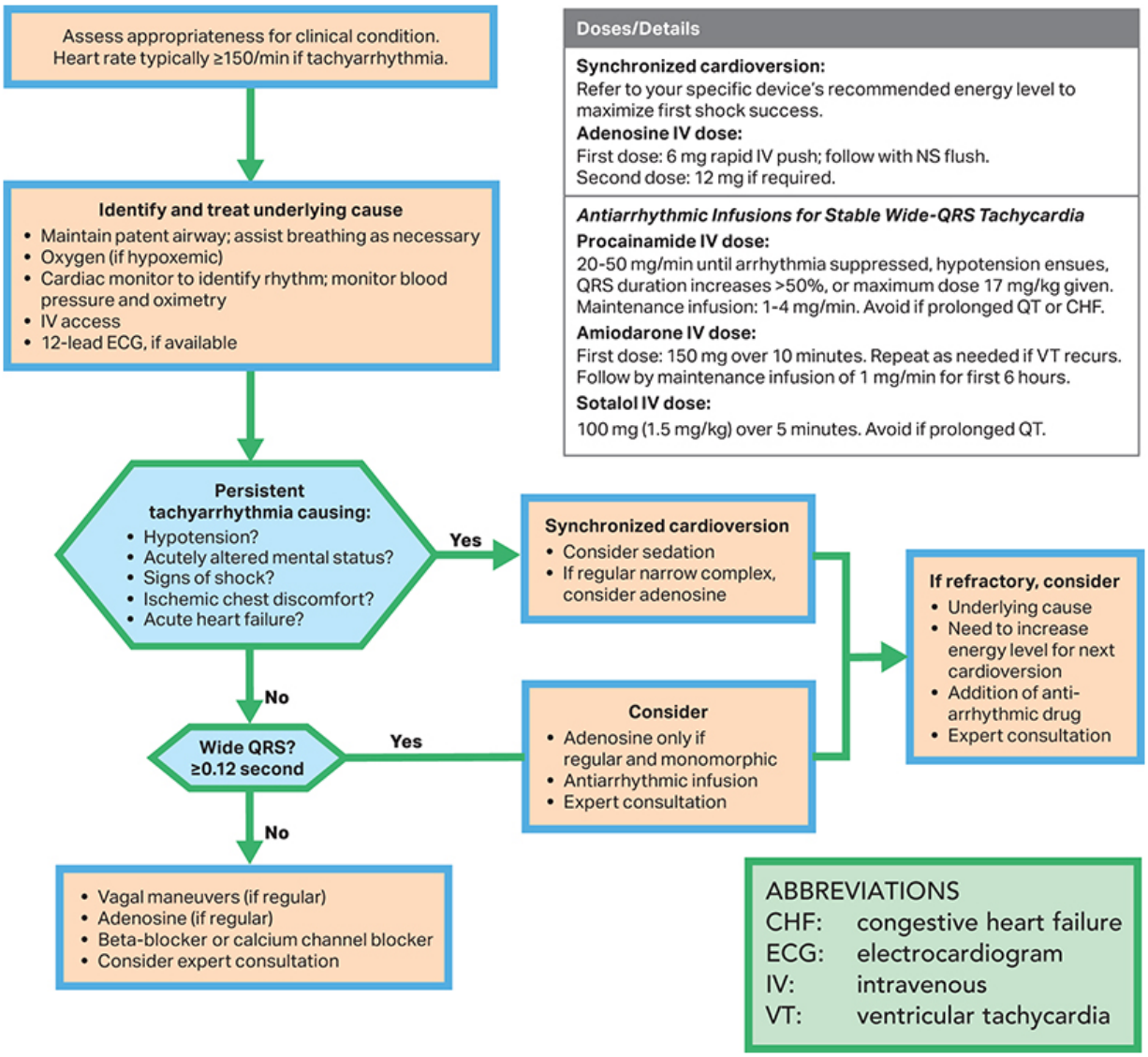
Updated definitions for diagnosing myocardial infarction in different clinical settings.

21 Cardiac Arrhythmias and Conduction Abnormalities

Philip C. Wiener, Sandeep S. Sodhi, and Daniel H. Cooper

This chapter addresses the causes, recognition, and treatment of cardiac arrhythmias occurring in patients who are hospitalized and critically ill. Cardiac arrhythmias can disrupt cardiac output (CO) by impairing the heart rate (HR) and/or stroke volume (SV)—evidenced by the equation CO = HR × SV. The clinical presentation of cardiac arrhythmias varies widely and may include (a) asymptomatic findings on an electrocardiogram (ECG) or telemetry, (b) symptoms without hemodynamic instability (eg, palpitations, shortness of breath, syncope, or chest pain), (c) hemodynamic instability in conscious patients, or (d) cardiac arrest. Initial evaluation in hospitalized patients includes ensuring (a) adequate airway and breathing support; (b) continuous monitoring of cardiac rhythm, blood pressure, and oxyhemoglobin saturation; (c) adequate intravenous (IV) access; and (d) adequate support personnel. The cardiac rhythm should be analyzed by 12-lead ECG when possible, but initial treatment may be based on the rhythm seen on the intensive care unit bedside monitor or external defibrillator. If time permits, the specific underlying rhythm should be identified, the cause sought, and therapy tailored accordingly. However, *severely symptomatic tachycardia, bradycardia, and cardiac arrest require immediate treatment based on the advanced cardiac life support (ACLS) algorithms* shown later in this chapter in Algorithms 21.1, 21.2, and 21.3.

ALGORITHM 21.1 Advanced Cardiac Life Support Tachycardia With a Pulse Treatment Algorithm


Assess appropriateness for clinical condition.
Heart rate typically ≥150/min if tachyarrhythmia.
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• Oxygen (if hypoxemic)
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
• IV access
• 12-lead ECG, if available
Persistent tachyarrhythmia causing:
• Hypotension?
• Acutely altered mental status?
• Signs of shock?
• Ischemic chest discomfort?
• Acute heart failure?
Yes
Synchronized cardioversion
• Consider sedation
• If regular narrow complex, consider adenosine
No
Wide QRS? ≥0.12 second
Yes
Consider
• Adenosine only if regular and monomorphic
• Antiarrhythmic infusion
• Expert consultation
No
• Vagal maneuvers (if regular)
• Adenosine (if regular)
• Beta-blocker or calcium channel blocker
• Consider expert consultation
If refractory, consider
• Underlying cause
• Need to increase energy level for next cardioversion
• Addition of anti-arrhythmic drug
• Expert consultation
Doses/Details
Synchronized cardioversion:
Refer to your specific device's recommended energy level to maximize first shock success.
Adenosine IV dose:
First dose: 6 mg rapid IV push; follow with NS flush.
Second dose: 12 mg if required.
Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia
Procainamide IV dose:
20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases >50%, or maximum dose 17 mg/kg given. Maintenance infusion: 1-4 mg/min. Avoid if prolonged QT or CHF.
Amiodarone IV dose:
First dose: 150 mg over 10 minutes. Repeat as needed if VT recurs. Follow by maintenance infusion of 1 mg/min for first 6 hours.
Sotalol IV dose:
100 mg (1.5 mg/kg) over 5 minutes. Avoid if prolonged QT.
ABBREVIATIONS
CHF: congestive heart failure
ECG: electrocardiogram
IV: intravenous
VT: ventricular tachycardia

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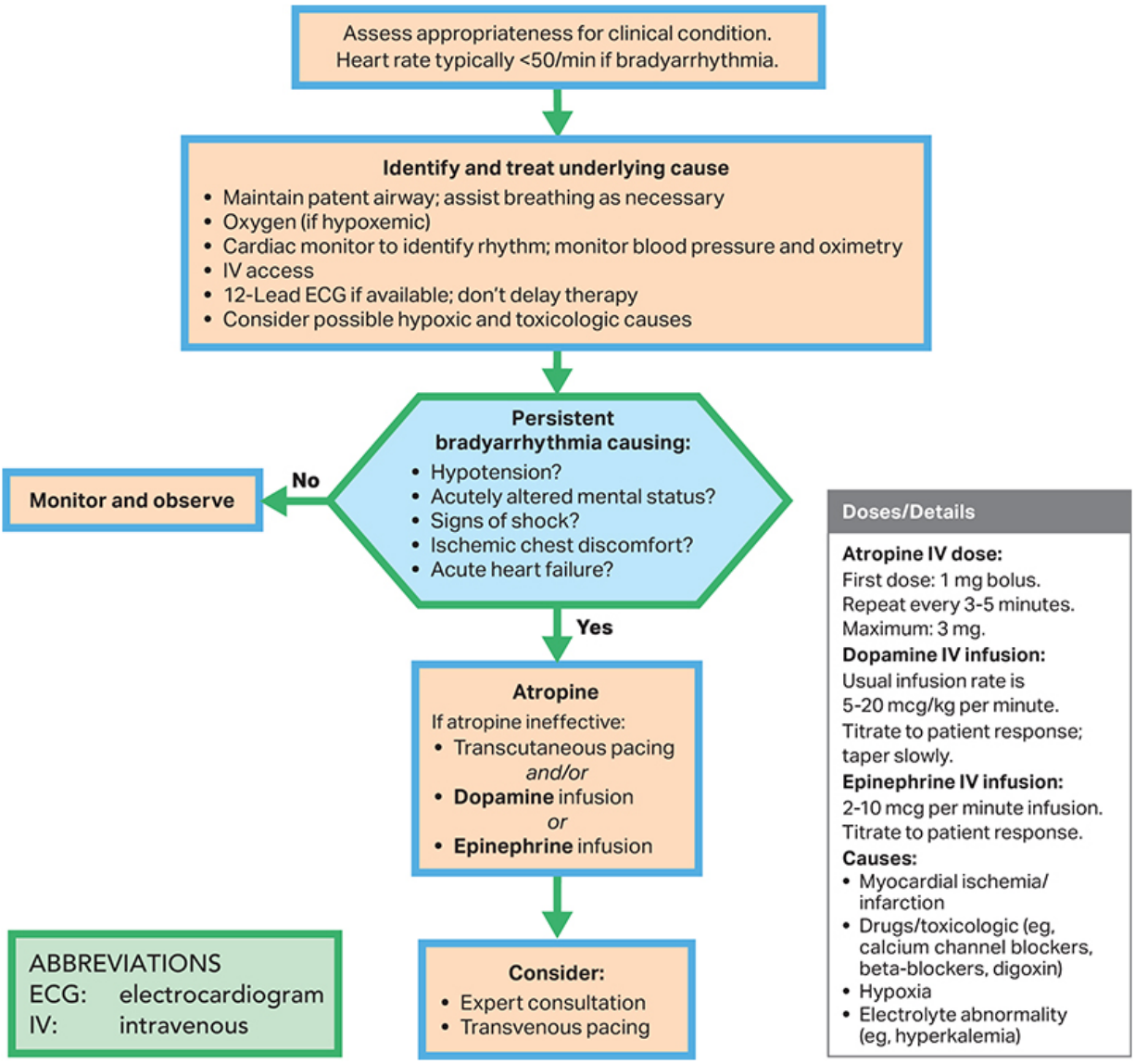
ALGORITHM 21.2 Advanced Cardiac Life Support Bradycardia Treatment Algorithm



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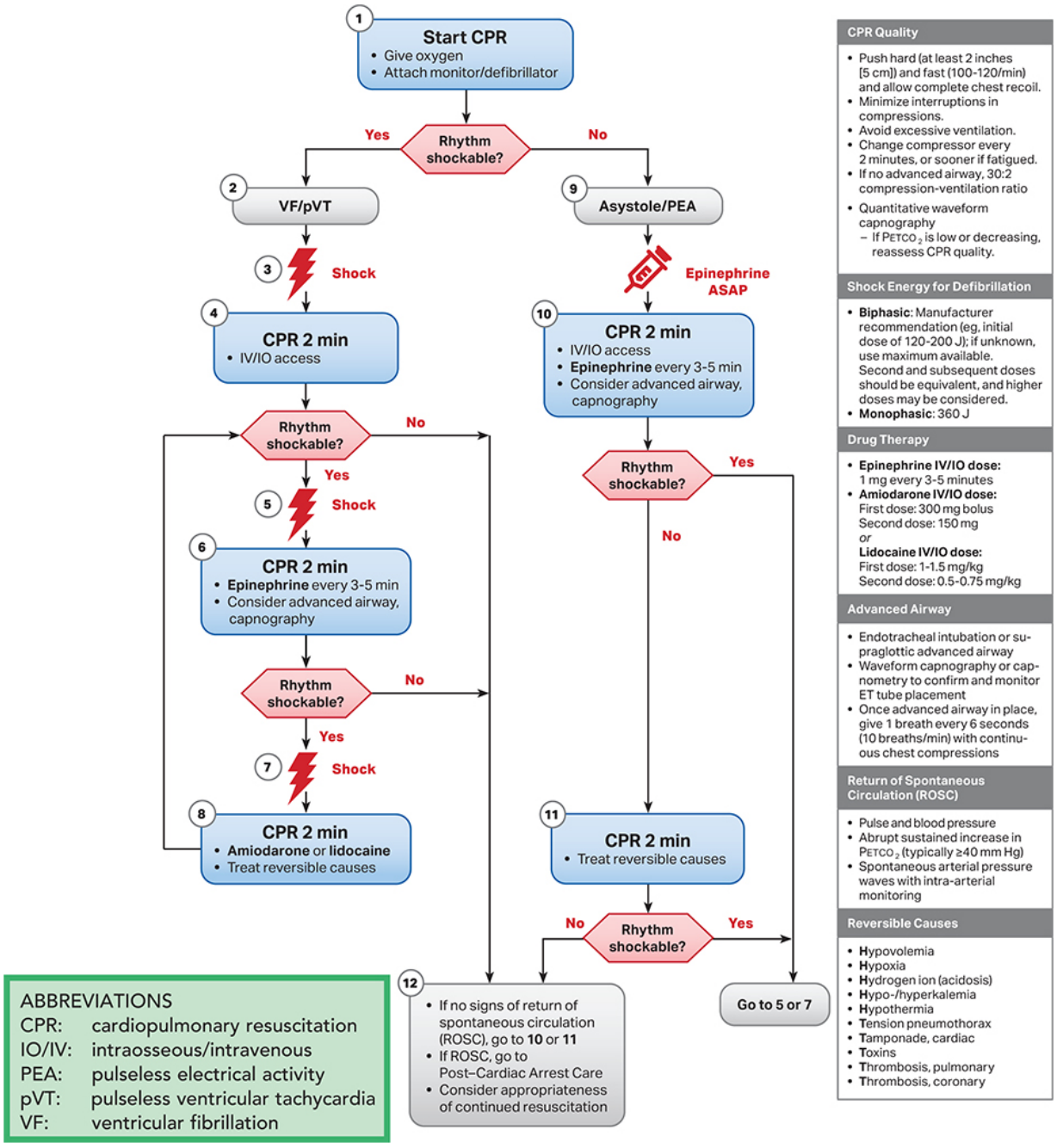
ALGORITHM 21.3 Advanced Cardiac Life Support Adult Cardiac Arrest Algorithm


1
Start CPR
• Give oxygen
• Attach monitor/defibrillator
Rhythm shockable?
Yes
No
2
VF/pVT
9
Asystole/PEA
3
Shock
Epinephrine ASAP
4
CPR 2 min
• IV/IO access
10
CPR 2 min
• IV/IO access
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
No
Yes
5
Shock
6
CPR 2 min
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
No
Yes
7
Shock
8
CPR 2 min
• Amiodarone or lidocaine
• Treat reversible causes
Rhythm shockable?
Yes
No
11
CPR 2 min
• Treat reversible causes
Rhythm shockable?
No
Yes
12
• If no signs of return of spontaneous circulation (ROSC), go to 10 or 11
• If ROSC, go to Post–Cardiac Arrest Care
• Consider appropriateness of continued resuscitation
Go to 5 or 7
ABBREVIATIONS
CPR: cardiopulmonary resuscitation
IO/IV: intraosseous/intravenous
PEA: pulseless electrical activity
pVT: pulseless ventricular tachycardia
VF: ventricular fibrillation
CPR Quality
• Push hard (at least 2 inches [5 cm]) and fast (100-120/min) and allow complete chest recoil.
• Minimize interruptions in compressions.
• Avoid excessive ventilation.
• Change compressor every 2 minutes, or sooner if fatigued.
• If no advanced airway, 30:2 compression-ventilation ratio
• Quantitative waveform capnography
– If PETCO2 is low or decreasing, reassess CPR quality.
Shock Energy for Defibrillation
• Biphasic: Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
• Monophasic: 360 J
Drug Therapy
• Epinephrine IV/IO dose: 1 mg every 3-5 minutes
• Amiodarone IV/IO dose: First dose: 300 mg bolus Second dose: 150 mg or Lidocaine IV/IO dose: First dose: 1-1.5 mg/kg Second dose: 0.5-0.75 mg/kg
Advanced Airway
• Endotracheal intubation or supraglottic advanced airway
• Waveform capnography or capnometry to confirm and monitor ET tube placement
• Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions
Return of Spontaneous Circulation (ROSC)
• Pulse and blood pressure
• Abrupt sustained increase in PETCO2 (typically ≥40 mm Hg)
• Spontaneous arterial pressure waves with intra-arterial monitoring
Reversible Causes
• Hypovolemia
• Hypoxia
• Hydrogen ion (acidosis)
• Hypo-/hyperkalemia
• Hypothermia
• Tension pneumothorax
• Tamponade, cardiac
• Toxins
• Thrombosis, pulmonary
• Thrombosis, coronary

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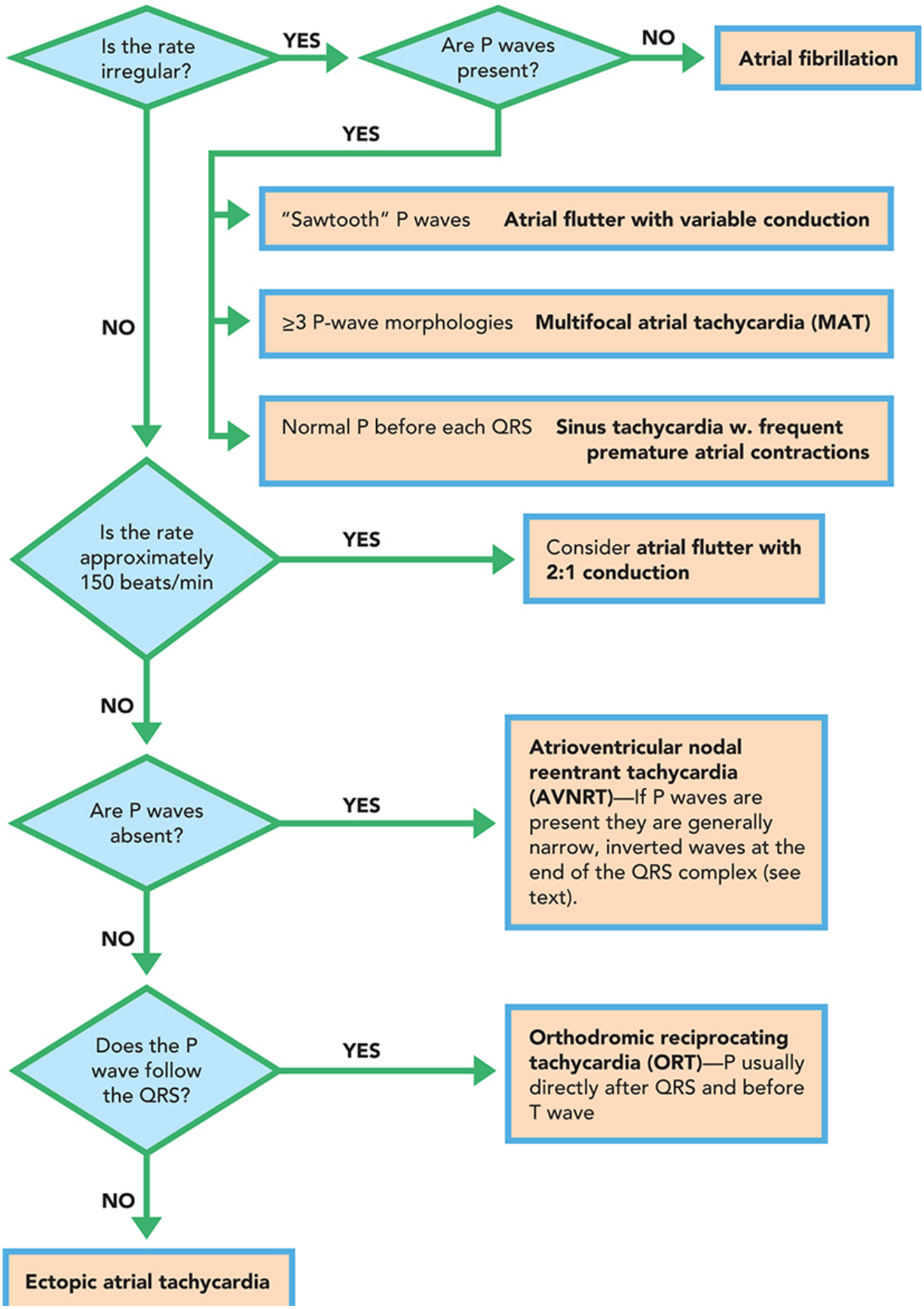
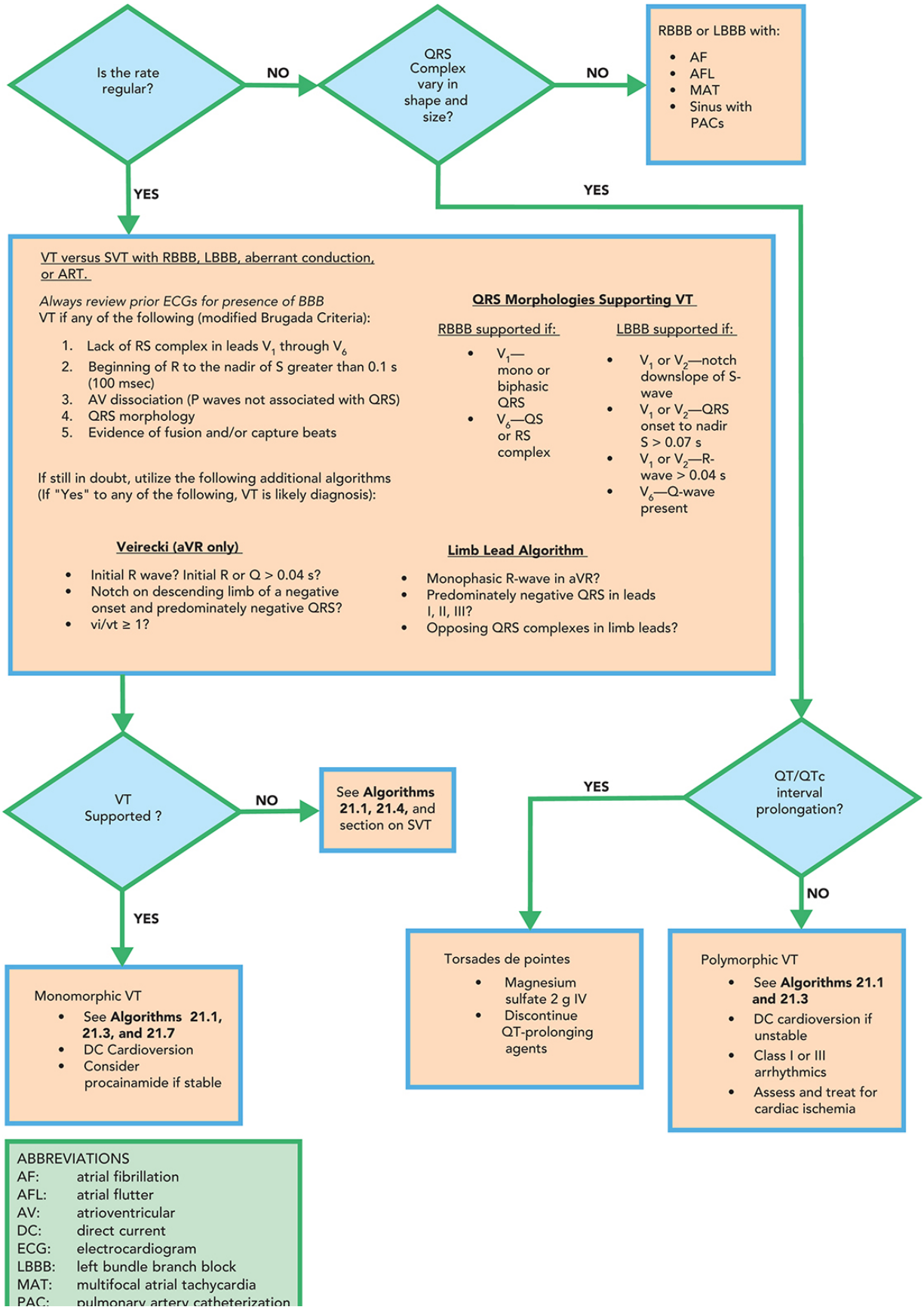
Tachyarrhythmias

Tachycardia, defined as an HR greater than 100 beats/min, can be separated into (a) those with origins above the ventricles, termed ***supraventricular tachycardias***, and (b) those that arise within the ventricles, termed ***ventricular tachycardias*** (***VTs***). Tachycardias can generally be distinguished based on the HR, the width and morphology of the QRS complex, and the length of the PR interval. The approach to differentiating narrow and wide QRS complex tachycardias is outlined in Algorithms 21.4 and 21.5, respectively.

ALGORITHM 21.4 Approach to Differentiating Narrow QRS Complex Tachycardias


Is the rate irregular?
YES
Are P waves present?
NO
Atrial fibrillation
YES
"Sawtooth" P waves
Atrial flutter with variable conduction
≥3 P-wave morphologies
Multifocal atrial tachycardia (MAT)
Normal P before each QRS
Sinus tachycardia w. frequent premature atrial contractions
NO
Is the rate approximately 150 beats/min
YES
Consider atrial flutter with 2:1 conduction
NO
Are P waves absent?
YES
Atrioventricular nodal reentrant tachycardia (AVNRT)—If P waves are present they are generally narrow, inverted waves at the end of the QRS complex (see text).
NO
Does the P wave follow the QRS?
YES
Orthodromic reciprocating tachycardia (ORT)—P usually directly after QRS and before T wave
NO
Ectopic atrial tachycardia

ALGORITHM 21.5 Approach to Differentiating Wide QRS Complex Tachycardias


Is the rate regular?
NO
QRS Complex vary in shape and size?
NO
RBBB or LBBB with:
AF
AFL
MAT
Sinus with PACs
YES
YES
VT versus SVT with RBBB, LBBB, aberrant conduction, or ART.
Always review prior ECGs for presence of BBB
VT if any of the following (modified Brugada Criteria):
1. Lack of RS complex in leads V1 through V6
2. Beginning of R to the nadir of S greater than 0.1 s (100 msec)
3. AV dissociation (P waves not associated with QRS)
4. QRS morphology
5. Evidence of fusion and/or capture beats
If still in doubt, utilize the following additional algorithms
(If "Yes" to any of the following, VT is likely diagnosis):
QRS Morphologies Supporting VT
RBBB supported if:
V1—mono or biphasic QRS
V6—QS or RS complex
LBBB supported if:
V1 or V2—notch downslope of S-wave
V1 or V2—QRS onset to nadir S > 0.07 s
V1 or V2—R-wave > 0.04 s
V6—Q-wave present
Veirecki (aVR only)
Initial R wave? Initial R or Q > 0.04 s?
Notch on descending limb of a negative onset and predominately negative QRS?
vi/vt ≥ 1?
Limb Lead Algorithm
Monophasic R-wave in aVR?
Predominately negative QRS in leads I, II, III?
Opposing QRS complexes in limb leads?
VT Supported ?
NO
See Algorithms 21.1, 21.4, and section on SVT
YES
Monomorphic VT
See Algorithms 21.1, 21.3, and 21.7
DC Cardioversion
Consider procainamide if stable
QT/QTc interval prolongation?
YES
NO
Torsades de pointes
Magnesium sulfate 2 g IV
Discontinue QT-prolonging agents
Polymorphic VT
See Algorithms 21.1 and 21.3
DC cardioversion if unstable
Class I or III arrhythmics
Assess and treat for cardiac ischemia
ABBREVIATIONS
AF: atrial fibrillation
AFL: atrial flutter
AV: atrioventricular
DC: direct current
ECG: electrocardiogram
LBBB: left bundle branch block
MAT: multifocal atrial tachycardia
PAC: pulmonary artery catheterization

PAC:	pulmonary artery catheterization
RBBB:	right bundle branch block
VT:	ventricular tachycardia
SVT:	supraventricular tachycardia

SUPRAVENTRICULAR TACHYCARDIAS

Sinus tachycardia originates from the sinus node and is not considered a primary arrhythmia. The ECG shows a normal P wave preceding each QRS complex, with upright morphology in lead II and a downward morphology in lead aVL. Sinus tachycardia in the intensive care unit can be a physiologic response to volume depletion, fever, pain, anxiety, shock, hypoxia, or in patients on vasopressor or inotropic support. Maximum heart rate (MHR) is age dependent and roughly limited to 220 − age in years (eg, in a 70-year-old man, MHR = 220 − 70 = 150).

Treatment of sinus tachycardia is directed at remedying the underlying cause, which includes treating infections and fever, repleting volume, administering anxiolytics as needed, and controlling pain. Rate-controlling agents are generally not indicated unless the tachycardia causes symptoms of low CO. Reflex sinus tachycardia may be important to maintain adequate CO. Direct treatment of the tachycardia without treatment of the underlying cause may be deleterious.

Atrial fibrillation is a chaotic rhythm within the atria of 350 to 600 beats/min without an appreciable P wave on ECG. All atrial beats are not conducted because of the refractory period in the atrioventricular (AV) node, and conduction is variably timed, resulting in an irregular ventricular rate. If the ventricular rate is greater than 100 beats/min, a rapid ventricular response is said to be present. The associated rapid HR and the lack of atrial contribution to pumping blood can compromise CO (primarily in patients with reduced cardiac function at baseline), requiring immediate treatment. Loss of organized atrial contraction creates stasis of the blood pool within the atria, which predisposes intracardiac thrombus formation and thromboembolism.

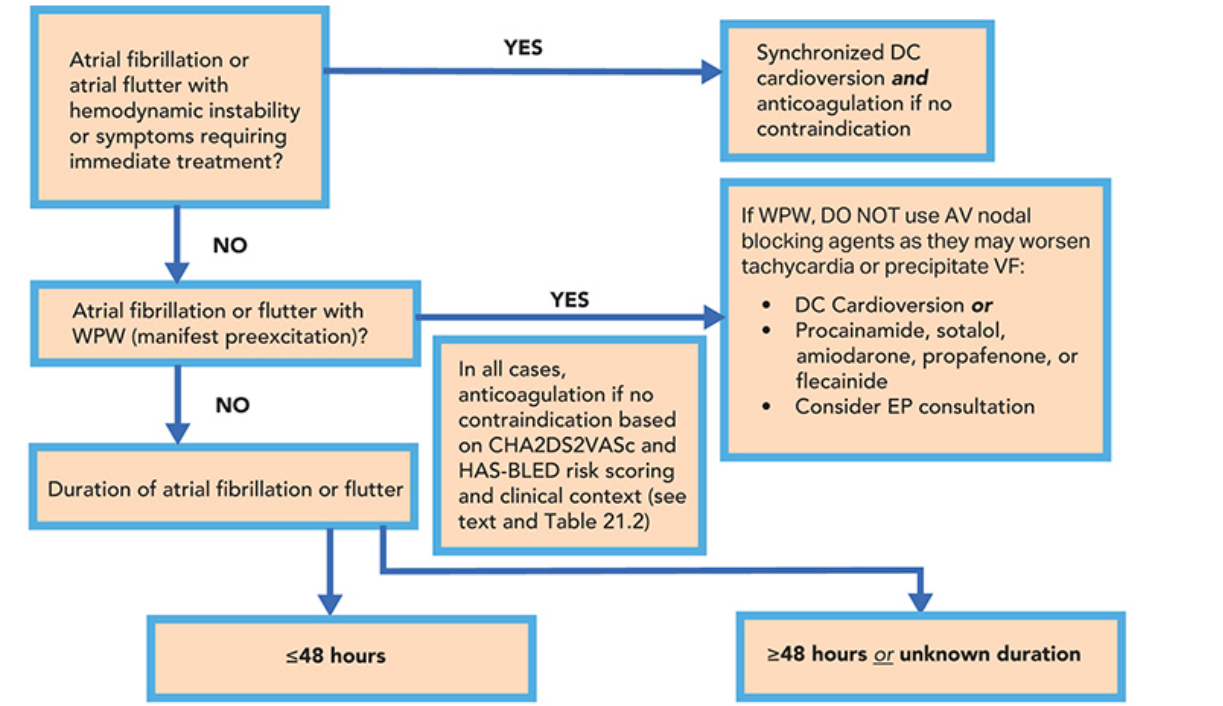
Atrial fibrillation is seen in association with chronic cardiopulmonary disease. It can also be the presenting finding of the older adults with conduction disturbances; patients with thyrotoxicosis, infection, pulmonary embolization, acute alcohol intoxication, pericarditis, and

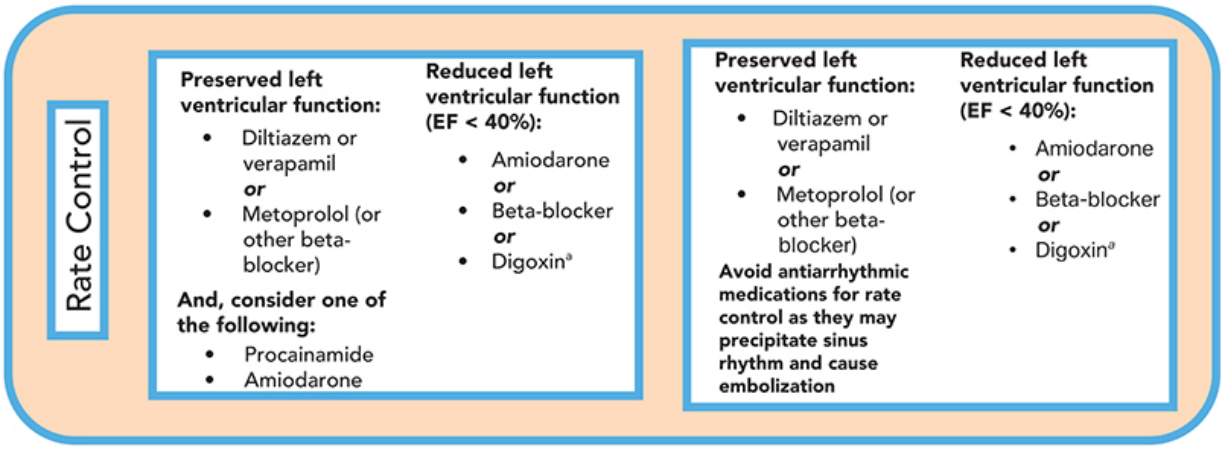
stress; and is common postoperatively. It is a rare presentation of acute myocardial infarction. It is classified based on the length of time the patient remains in a singular episode of atrial fibrillation. *Paroxysmal*, an episode lasting less than 7 days; *persistent*, an episode lasting greater than 7 days with the continued pursuit of rhythm control; and *permanent*, an episode sustaining longer than 1 year with a shared decision to forgo restoration of sinus rhythm.

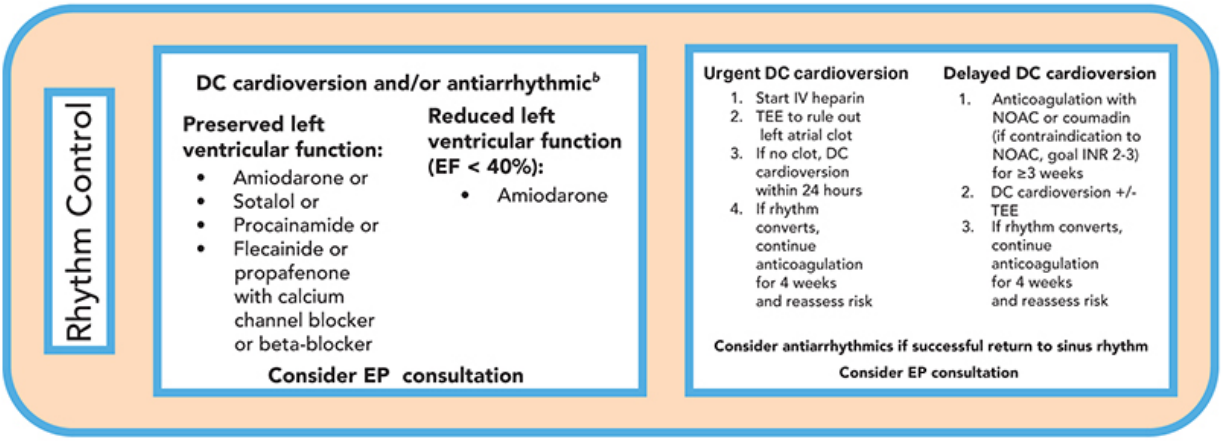
Typical ***atrial flutter*** is caused by a macro-reentrant rhythm localized to the right atrium, often dependent on the cavotricuspid isthmus, which generates impulses at a rate of approximately 300 beats/min. The ventricular rate is frequently 150 beats/min (half the atrial rate) due to a 2:1 block within the AV node. In the 3:1 block, every third beat is conducted, and the ventricular rate is approximately 100 beats/min. A large portion of the atria is depolarized at once, causing a classic "sawtooth" appearance on the baseline of the ECG, with fairly narrow, negative flutter waves in the inferior leads (II, III, and aVF). The ventricular rate may be regular, but can be irregular if conduction is variable (ie, 2:1 alternating with 3:1). It is seen in patients with underlying heart disease, following cardiac surgery, or following catheter-based ablation procedures. If left untreated, atrial flutter may degrade to atrial fibrillation.

Initial management of atrial fibrillation and atrial flutter is outlined in Algorithm 21.6. Precipitating factors should be sought and treated. Preoperative beta-blockers can reduce the incidence of postoperative atrial fibrillation/flutter. For atrial fibrillation or flutter that persists despite electrical cardioversion and/or pharmacotherapy, consider electrophysiology consultation for evaluation of ablation procedures (see Table 21.1).

ALGORITHM 21.6 **Treatment of Atrial Fibrillation and Atrial Flutter (See Chapter 95, Common Drug Dosages and Side Effects)**


Atrial fibrillation or atrial flutter with hemodynamic instability or symptoms requiring immediate treatment?
YES
Synchronized DC cardioversion and anticoagulation if no contraindication
NO
Atrial fibrillation or flutter with WPW (manifest preexcitation)?
YES
If WPW, DO NOT use AV nodal blocking agents as they may worsen tachycardia or precipitate VF:
• DC Cardioversion or
• Procainamide, sotalol, amiodarone, propafenone, or flecainide
• Consider EP consultation
NO
In all cases, anticoagulation if no contraindication based on CHA2DS2VASc and HAS-BLED risk scoring and clinical context (see text and Table 21.2)
Duration of atrial fibrillation or flutter
≤48 hours
≥48 hours or unknown duration




Rhythm Control
DC cardioversion and/or antiarrhythmic[b]
Preserved left ventricular function:
• Amiodarone or
• Sotalol or
• Procainamide or
• Flecainide or propafenone with calcium channel blocker or beta-blocker
Reduced left ventricular function (EF < 40%):
• Amiodarone
Consider EP consultation
Urgent DC cardioversion
1. Start IV heparin
2. TEE to rule out left atrial clot
3. If no clot, DC cardioversion within 24 hours
4. If rhythm converts, continue anticoagulation for 4 weeks and reassess risk
Delayed DC cardioversion
1. Anticoagulation with NOAC or coumadin (if contraindication to NOAC, goal INR 2-3) for ≥3 weeks
2. DC cardioversion +/- TEE
3. If rhythm converts, continue anticoagulation for 4 weeks and reassess risk
Consider antiarrhythmics if successful return to sinus rhythm
Consider EP consultation

ABBREVIATIONS

DC: direct current
EF: ejection fraction
EP: electrophysiology
INR: international normalized ratio
IV: intravenous
TEE: transesophageal echocardiogram
WPW: Wolff-Parkinson-White

[a]Caution when using digoxin due to narrow therapeutic window and strict renal function requirements. [b]Premedicate when possible with a sedative (eg, diazepam, midazolam, ketamine, etomidate) and analgesic (eg, fentanyl, morphine). Perform synchronized cardioversion with 100 J, 200 J, 300 J, 360 J, biphasic energy or monophasic equivalent, starting with the lowest energy level and increasing if needed. Perform asynchronous cardioversion if delays in synchronized cardioversion with worsening clinical status.

TABLE 21.1 ACLS Pharmacotherapies: Dosing and Side Effects

Medications	IV Dosing	Side Effects
Metoprolol	SVT: 2.5-5 mg IV q5 min (max dose 15 mg over 15 min)	Hypotension, bradycardia, bronchoconstriction, CHF
Diltiazem	SVT: 0.25 mg/kg IV over 2 min, repeat bolus (after 15 min if response inadequate) 0.35 mg/kg IV over 2 min	Hypotension, bradycardia, CHF
Adenosine	SVT: initial dose: 6 mg IV rapid push	Flushing, headache, AV block, asystole
	Repeat bolus (after 2 min if response inadequate) 12 mg IV rapid push (always flush with saline)	
Digoxin	SVT: initial loading dose: 0.25-0.5 mg IV slow push (reduce dose by 50% in renal failure), up to 1.5 mg in 24 h	Atrial tachycardia with or without AV block, nausea, blurred vision

Medications	IV Dosing	Side Effects
Epinephrine (1:10,000)	PEA/asystole: 1 mg IV q3-5 min × 3 doses (higher doses or continuous infusions can be used to treat specific problems)	Tachyarrhythmias, chest pain, hypertension
Vasopressin	PEA/asystole: 40 units IV may replace the first or second dose of epinephrine.	Tachyarrhythmias, asystole, chest pain, hypertension
Atropine	Slow PEA/asystole: 1 mg IV q3-5 min × 3 doses Bradycardia: 0.5-1 mg IV q3-5 min, up to 0.04 mg/kg in 24-h period	Anticholinergic side effects, tachyarrhythmias, hypotension
Dopamine	Hemodynamic support: 1-5 mcg/kg/min, max dose 50 mcg/kg/min	Vasoconstriction, arrhythmias, hypotension (at lower doses), chest pain
Norepinephrine	Hemodynamic support: 0.5-1 mcg/min, max dose titrate to response	Vasoconstriction, arrhythmias, chest pain
Amiodarone	300 mg IV push, can redose if inadequate response 150 mg IV push	Hypotension, prolonged QT interval, bradycardia arrhythmias
Lidocaine	1-1.5 mg/kg IV over 2-3 min, may repeat 0.5-0.75 mg/kg IV q10 min for a total of 3 doses	Tachyarrhythmias, bradycardia, hypotension, AV block
Procainamide	20-50 mg/min until arrhythmia controlled	Hypotension, lupus-like syndrome, QRS widening
Magnesium	Torsades de pointes: 1-2 mg IV push over 5-20 min	Flushing, hypotension

ACLS, advanced cardiac life support; CHF, congestive heart failure; IV, intravenous; SVT, supraventricular tachycardia.

Thromboembolic risk stratification and bleeding risk must be assessed for each patient noted in Table 21.2. Acute thromboembolic risk management typically involves anticoagulation with IV heparin. Long-term anticoagulation can be achieved by transitioning to a non-vitamin K oral anticoagulant (NOAC) such as apixaban, rivaroxaban, edoxaban, or dabigatran. These NOACs are appropriate in patients with atrial fibrillation or atrial flutter who do not possess a mechanical cardiac valve or moderate-to-severe mitral valve stenosis. If a patient does possess a mechanical cardiac valve or moderate-to-severe mitral valve stenosis, overlapping transition to warfarin with a goal international normalized ratio (INR) greater than 2 is indicated.

TABLE 21.2 Stroke Risk and Bleeding Risk Assessment

CHA2DS2VASc Risk Score		HAS-BLED Risk Score	
Criteria	**Points**	**Criteria**	**Points**
Congestive heart failure history	+1	**H**ypertension (SBP ≥ 160)	+1
Hypertension	+1	**A**bnormal renal function (HD, transplant, Cr > 2.26 mg/dL)	+1
Age 65-74	+1	**A**bnormal liver function (cirrhosis, elevated bilirubin/transaminases)	+1
Age ≥ 75	+2	**S**troke history	+1
Diabetes mellitus	+1	**B**leeding (major or predisposition)	+1
Stroke or thromboembolic history	+2	**L**abile INR	+1
Vascular disease	+1	Older adults (age > 65)	+1
Gender (* +1 if female)	*	**D**rugs (NSAIDs, antiplatelet, etc)	+1

CHA2DS2VASc Risk Score		HAS-BLED Risk Score	
Criteria	**Points**	**Criteria**	**Points**
			+1
		Alcohol use (≥8 drinks per week)	
Score ≥2 (≥3 if Female): benefit from stroke risk reduction with anticoagulation		Each point increases the risk of major bleeding.	

HD, hemodialysis; INR, international normalized ratio; NSAIDs, non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure.

Paroxysmal supraventricular tachycardias (PSVT) are characterized by sudden onset and termination. The most common PSVT in adults is ***AV nodal reentrant tachycardia*** (AVNRT). It is caused by a reentrant electrical loop within the AV node. The rate generally varies from 120 to 250 beats/min and is associated with a narrow QRS complex in the absence of aberrancy or an underlying bundle branch block. The atria and ventricles typically depolarize at virtually the same time; thus, the P waves are frequently not visible, obscured by the QRS complexes. If visible, they generally present as narrow inverted P waves at the end of the QRS complex, commonly described as a “pseudo R” in V1 and/or “a pseudo S” in lead II. AVNRT is not typically associated with specific diseases, can occur at any age, and is more common in women.

PSVT may also be mediated by an accessory pathway between the atria and ventricles that bypasses the AV node. *Manifest* accessory pathways are seen on the sinus rhythm ECG as a “delta wave” of preexcitation. The preexcitation also causes a short PR interval because the accessory pathway does not have the delayed conduction of the AV node. Accessory pathways may conduct antegrade (forming the delta wave) or retrograde. *Concealed* accessory AV pathways only conduct retrograde and are invisible in sinus rhythm. Either of these

pathways may mediate an ***orthodromic reentrant tachycardia*** (***ORT***) in which the electrical impulse propagates antegrade through the AV node and retrograde (from ventricle to atrium) through the accessory pathway. The result is a narrow QRS complex tachycardia, typically with inverted, retrograde P waves between the QRS and T wave (although the QRS may be wide because of aberrancy, eg, bundle branch block or fascicular block).

The patient with visible preexcitation (delta wave and short PR interval) in sinus rhythm and with palpitations (usually from paroxysmal ORT) is said to have ***Wolff-Parkinson-White syndrome*** (WPW). Patients with WPW are also prone to arrhythmias with antegrade conduction through the accessory pathway. These include ***antidromic reentrant tachycardia***, in which the excitation propagates antegrade through the accessory pathway and retrograde through the AV node. Atrial arrhythmias (including atrial fibrillation) may also conduct antegrade through the accessory pathway. The short refractory period of the accessory pathway may allow very rapid conduction of impulses to the ventricles, resulting in rapid “preexcited atrial fibrillation” with ventricular rates up to 300 beats/min, often resulting in hemodynamic instability requiring urgent intervention. Rapid conduction of atrial fibrillation through an accessory pathway may also induce ventricular fibrillation (VF). This is thought to be the pathogenesis of the rare sudden death that is associated with WPW.

Treatment of PSVT aims at aborting the reentrant rhythm by blocking conduction through the AV node with vagal maneuvers (Valsalva, carotid massage, and face immersion in cold water [diving reflex]) or adenosine given as a 6-mg IV bolus ($t_{1/2}$ ~ 10 seconds). A second 12-mg dose can be given after 1 to 2 minutes if the first was ineffective, and a third dose of 12 or 18 mg can be given if needed. If these treatments fail, AV nodal blocking agents, calcium channel blockers, or digoxin should be used. Patients with WPW and preexcited atrial fibrillation or flutter must be rapidly treated with direct current cardioversion or class IA, IC, or III drugs (eg, procainamide, flecainide, and amiodarone), which slow myocardial conduction and prolong the refractory period. AV nodal blocking agents are not to be used as they may shorten the refractory period of ventricular

myocardium and when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction, which may precipitate VT/VF (Algorithm 21.6). Advanced management of PSVT includes evaluation by electrophysiology for potential ablative therapy targeting the mechanism of arrhythmia.

Ectopic atrial tachycardia occurs when there is automaticity at a single focus outside the sinoatrial (SA) node. A P wave precedes each QRS as in sinus tachycardia, but the P-wave axis and morphology are typically altered. When increased automaticity occurs at three or more different atrial sites, which may include the SA node, it is termed ***multifocal atrial tachycardia***, with the alternating foci causing at least three P-wave morphologies on ECG. Both can be seen in cases of digitalis toxicity (which causes increased automaticity), severe cardiopulmonary disease, hypokalemia, hyperadrenergic states, and as a side effect of theophylline. Treatment includes AV nodal blocking agents and removal of inciting agents/factors (ie, chronic obstructive pulmonary disease exacerbations, infections, and stimulants).

VENTRICULAR TACHYCARDIAS

The two main tachyarrhythmias arising from the ventricles are ***ventricular tachycardia*** (VT) and ***ventricular fibrillation*** (VF). VT may be monomorphic, if the QRS morphology is fixed, or polymorphic, if the QRS complex is variable. Polymorphic VT results in chaotic ventricular activation, often with hemodynamic instability, possibly leading to cardiac arrest and sudden death. It is more likely to occur in the setting of acute ischemia, infarction, or acute heart failure.

Monomorphic VT results from reentrant electrical impulses within the ventricles or from a focal site with frequent spontaneous action potentials that propagate to the remainder of the ventricles. VT is characterized on ECG by a wide QRS complex (>0.12 seconds) and a rate usually between 100 and 200 beats/min (although it may be higher). VT lasting less than 30 seconds is termed *nonsustained VT* (NSVT), while sustained VT lasts greater than 30 seconds. The most common substrates for monomorphic VT are healed myocardial infarction or significant cardiomyopathy. It occurs less commonly in acute ischemia or active infarction. Importantly, monomorphic VT may

occur in the absence of structural heart disease. These “idiopathic VTs” do not have a poor prognosis and may not cause hemodynamic instability, emphasizing the need to assess and treat the patient’s condition, and not solely the ECG.

An important type of polymorphic VT is ***torsades de pointes***, characterized by polymorphic VT associated with prolongation of the QT interval (in sinus rhythm) and early after depolarizations in Phase 2 of the action potential. It may be related to numerous causes, including (a) drugs (especially tricyclic antidepressants, antipsychotics, certain antiarrhythmics, macrolides, and fluoroquinolones), (b) electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), and (c) congenital long QT syndromes. Torsades de pointes appears on ECG as a characteristic pattern of oscillating amplitude of the QRS, or “twisting,” around the baseline. Torsades de pointes is generally symptomatic but may be nonsustained. If prolonged, hemodynamic instability, syncope, and/or sudden death may result.

Wide complex tachycardias (except clear sinus tachycardia with aberrancy) should initially be assumed to be VT, and the urgency of treatment should depend on assessment of the patient and the hemodynamic situation. Distinguishing VT from supraventricular tachycardia (SVT) with a wide QRS is therefore of secondary importance. Mistaken diagnosis of “SVT with aberrancy” can result in mistreatment. The differential diagnosis of wide complex tachycardia is 3-fold: (a) VT, (b) SVT with aberrancy (typical bundle branch or fascicular blocks or atypical aberrancy), and (c) preexcited supraventricular rhythm (including atrial fibrillation)—in which case the ECG in sinus rhythm will typically feature a delta wave.

Algorithm 21.5 reviews the ECG criteria that favor VT. Also, old ECGs should be examined for bundle branch blocks or ventricular preexcitation syndromes. As previously mentioned, if the diagnosis of the wide complex rhythm is uncertain, it should be assumed to be VT, and treatment should proceed according to the patient’s condition.

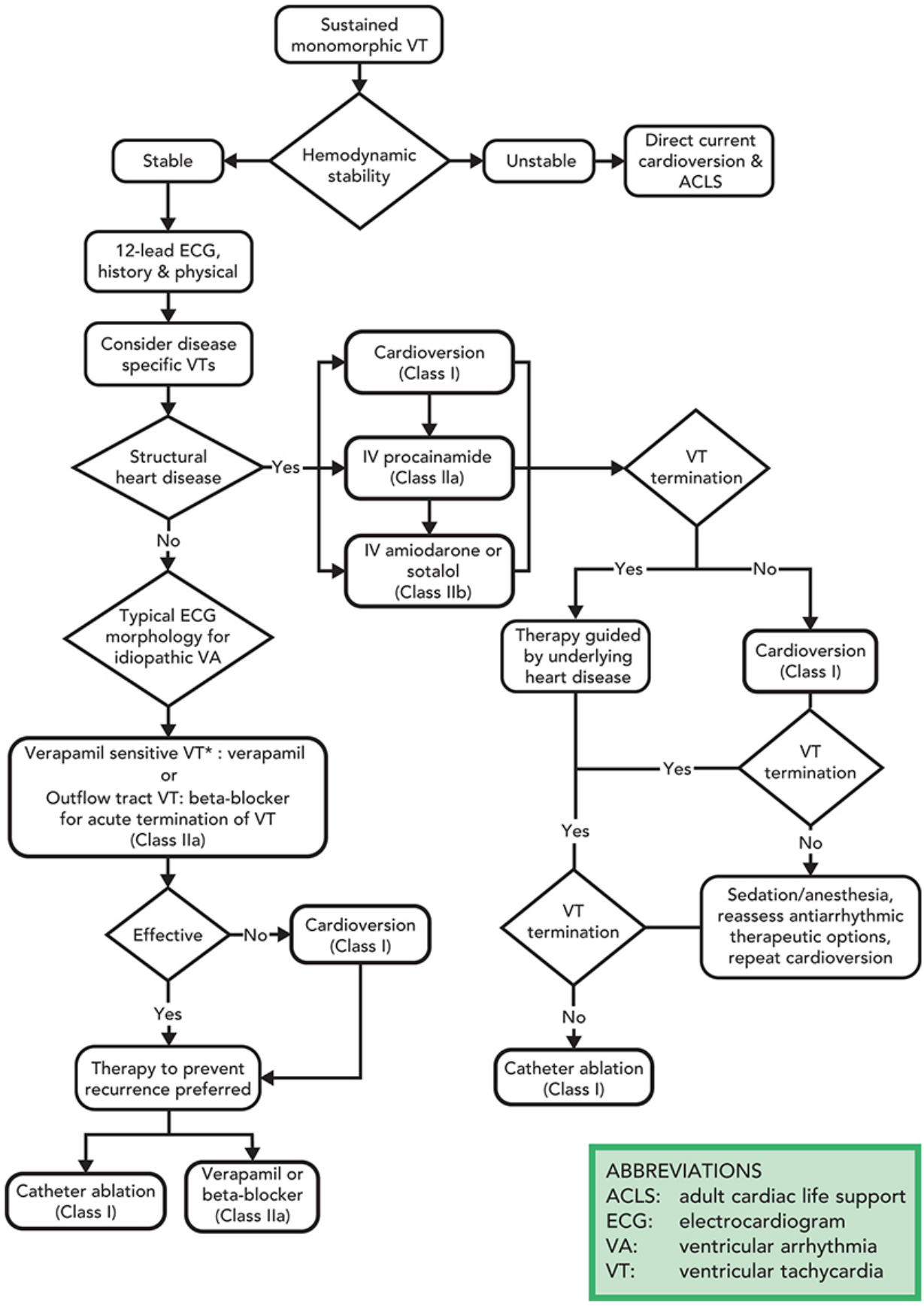
NSVT may be idiopathic or occur in the setting of acute ischemia or heart failure, and evaluation and treatment should be focused on the underlying etiology if one is present. Direct pharmacologic treatment (eg, lidocaine, amiodarone) of NSVT in ischemia/infarct is not advisable. If the patient is not suffering from ischemia, NSVT can

frequently be asymptomatic and has little prognostic utility for malignant arrhythmia, especially in the absence of structural heart disease and ventricular dysfunction. Symptomatic NSVT may be treated pharmacologically with beta-blockers, primarily to relieve symptoms.

Sustained VT generally causes symptoms by impairing CO, resulting in hypotension, loss of consciousness, and possibly cardiac arrest. It may also deteriorate into VF. VT or VF storm is an electrical condition associated with refractory VT/VF defined by greater than or equal to 3 episodes of sustained VT, VF, or appropriate shocks from an implantable cardioverter-defibrillator (ICD).

Treatment of symptomatic VT with a detectable pulse is *synchronous* direct current cardioversion (with sedation or anesthesia in the awake patient) or, if the VT is hemodynamically tolerated by the patient, with an antiarrhythmic drug (such as amiodarone or lidocaine). Patients with hemodynamically compromising, pulseless monomorphic, or polymorphic VT usually require immediate treatment with asynchronous defibrillation (see “Cardiac Arrest” section), followed by antiarrhythmic drugs if necessary. Once the patient is stable, consideration should be given to VT ablation in addition to antiarrhythmic medications for long-term management of VT and to prevent further defibrillation therapy. Algorithm 21.7 describes the evaluation and treatment of monomorphic sustained VT.

ALGORITHM 21.7 Management of Sustained Monomorphic Ventricular Tachycardia



ABBREVIATIONS

ACLS:	adult cardiac life support
ECG:	electrocardiogram
VA:	ventricular arrhythmia
VT:	ventricular tachycardia

*Known history of verapamil sensitive or classical electrocardiographic presentation
Reprinted with permission Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation*. 2018;138:e272-e391 ©2017 American Heart Association, Inc.

Sustained torsades de pointes with hemodynamic collapse also requires asynchronous cardioversion. Treatment of torsades de pointes aims at correcting any underlying electrolyte abnormalities (ie, magnesium, potassium) and stopping any drugs known to prolong the QT interval. Torsades de pointes is likely to recur if the inciting factors cannot be eliminated immediately. Lidocaine or phenytoin may also be suppressive. Torsades de pointes is frequently *bradycardia dependent*, and temporary pacing or isoproterenol infusion may be used to increase the HR and prevent recurrences.

VF is the result of chaotic electrical currents within the ventricles, preventing coordinated contractions. VF on ECG has a chaotic appearance without any discernable QRS complex. Untreated VF rapidly results in death. VF may be preceded by VT and is most commonly seen in patients with acute myocardial infarction or profound heart failure.

Treatment is immediate asynchronous electrical defibrillation, followed by antiarrhythmic drugs when a stable rhythm returns (see “Cardiac Arrest” section). Treatment Algorithm 21.3 outlines the management of VF in the setting of cardiac arrest. Increasingly, ablation procedures are being employed for the management of VF. VF triggered by PVCs, in particular, can be targeted for ablation once the patient has been stabilized. Patients who survive with meaningful recovery cardiac arrest caused by any ventricular arrhythmia should be evaluated for secondary prevention ICD prior to hospital discharge.

Bradyarrhythmias

Bradycardia, defined as an HR of less than 60 beats/min, occurs from (a) SA node dysfunction or (b) disturbances of the AV conduction

system. Clinically significant bradycardia occurs when there is inadequate CO, generally associated with hypotension, and may manifest as presyncope, syncope, fatigue, confusion, depressed level of consciousness, chest pain, shock, and/or congestive heart failure. Appropriate management entails identifying the underlying rhythm and cause of the bradycardia. Acute treatment aims at restoring adequate CO and its cause.

SA node dysfunction occurs in a number of pathophysiologic states seen in the intensive care unit, including increased intracranial pressure, prolonged apneic periods in patients with obstructive sleep apnea/hypopnea syndrome, myocardial infarction, advanced liver disease, hypothyroidism, hypothermia, hypercapnia, acidemia, hypervagotonia, and certain infections. It may also be due to depression of the sinus node by drugs, including sympatholytics such as beta-blockers and clonidine, the cardioselective calcium channel blockers verapamil and diltiazem, parasympathomimetics, and antiarrhythmic drugs such as amiodarone (Tables 21.3 and 21.4). Sick sinus syndrome refers to intrinsic sinus node dysfunction with any of the previously mentioned clinical symptoms resulting in decreased CO. An important variant of sick sinus syndrome is associated with sinus bradycardia or prolonged sinus pause occurring after termination of atrial fibrillation or other atrial arrhythmias due to depression of SA node automaticity during the tachyarrhythmia, which may be slow to recover. Syncope or near-syncope is a common presentation of this variant, termed the ***tachy-brady syndrome***.

TABLE 21.3 Medications That Induce or Worsen Bradycardia and Conduction Disorders

Antihypertensive	Antiarrhythmic	Psychoactive	Other

Antihypertensive	Antiarrhythmic	Psychoactive	Other
• Beta-adrenergic receptor blockers (including beta-adrenergic blocking eyedrops for glaucoma) • Clonidine • Methyldopa • Non-dihydropyridine calcium channel blockers • Reserpine	• Adenosine • Amiodarone • Dronedarone • Flecainide • Procainamide • Propafenone • Quinidine • Sotalol	• Donepezil • Lithium • Opioid analgesics • Phenothiazine antiemetics and antipsychotics • Phenytoin • Selective serotonin reuptake inhibitors • Tricyclic antidepressants	• Anesthetic drugs (propofol) • Cannabis • Digoxin • Ivabradine • Muscle relaxants (succinylcholine)

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TABLE 21.4 Etiologies of Bradycardia

Intrinsic	Extrinsic

Intrinsic	Extrinsic
• Cardiomyopathy (ischemic or nonischemic) • Collagen vascular disorders such as rheumatoid arthritis, scleroderma, or systemic lupus erythematosus • Congenital disease (any age) • Idiopathic degeneration (aging) • Infectious diseases such as Chagas disease, endocarditis, or Lyme disease • Infiltrative diseases such as amyloidosis, hemochromatosis, or sarcoidosis • Ischemia or infarction • Surgical trauma such as transplantation or valve intervention (surgical or procedural)	• Autonomic mediation • Carotid sinus hypersensitivity • Drugs such as antiarrhythmic medications, beta-blockers, calcium channel blockers, or digoxin • Electrolyte imbalances such as hyperkalemia, hypomagnesemia • Hypercarbia • Hypothermia • Hypothyroidism • Increased vagal tone such as coughing, defecation, micturition, intubation, or vomiting • Neurocardiogenic syncope • Neurologic disorders such as increased intracranial pressure • Obstructive sleep apnea • Sepsis

Disturbances of the AV conduction system can occur in the atria, AV node, or His-Purkinje system. When there is a complete block in any part of the AV conduction system (termed ***third-degree AV block***), an escape pacemaker generally develops. When a complete blockage occurs in the AV node, the His bundle escape pacemaker generally takes over at a rate of 40 to 60 beats/min and is associated with a narrow QRS complex (in the absence of an underlying bundle branch block or other aberrant conduction). Complete heart block distal to the AV node often results in an escape pacemaker originating from the more distal conduction system, usually with a rate between 25 and 45 beats/min. These fascicular escape rhythms generate a QRS complex consistent with their origin (eg, if the origin is in the right bundle, the QRS has a left bundle branch block pattern). If the conduction system fails, a rhythm from the ventricular myocardium may generate a heartbeat, with a wide complex of ventricular origin. Thus, in general, the more distal the escape rhythm, the slower and less reliable it tends

to be. Heart block with irregular fascicular escapes may require urgent temporary pacing. The ECG shows AV dissociation with nonconducted P waves that “march” out independently of the ventricular escape rhythm, enough time for the P wave to theoretically conduct to the ventricle, and commonly more P waves than QRS complexes. There are many causes of third-degree heart block including acute myocardial infarction, idiopathic fibrosis, drug toxicity (eg, digitalis, beta-blockers, cardioselective calcium channel blockers), chronic cardiopulmonary disease, congenital heart disease, infiltrative diseases (sarcoidosis), infections/inflammatory diseases, collagen vascular diseases, trauma, and tumors (Tables 21.3 and 21.4).

First-degree AV block is not truly heart *block* but rather represents a delay in normal cardiac conduction. It is defined by a PR interval greater than 200 ms. First-degree AV block is generally benign but may result in symptoms if the degree of AV dyssynchrony is severe.

Second-degree AV block occurs when some atrial impulses fail to conduct to the ventricles. **Second-degree, type 1 AV block** (alternatively known as Mobitz type I second-degree AV block or Wenckebach block) is characterized on ECG by a variable (usually progressively prolonging) PR interval culminating in a nonconducted atrial beat. Second-degree, type 1 AV block uncommonly progresses to complete heart block. When it does, the escape pacemaker of 40 to 60 beats/min in the His bundle usually provides an adequate backup rate to maintain CO. Second-degree, type 1 AV block can be caused by drugs such as digoxin, beta-blockers, certain calcium channel blockers, or by ischemia (especially of the inferior wall) or hypervagotonia in otherwise healthy individuals.

Second-degree, type 2 AV block (alternatively known as Mobitz type II second-degree AV block) generally is due to disease in the His-Purkinje system and is characterized on ECG by a fixed PR interval with one or more nonconducting atrial impulses. It is more likely to progress, sometimes precipitously, to a complete heart block than a second-degree, type 1 AV block. The typical escape pacemaker rate of 25 to 45 arises in the more distal His-Purkinje system and has a wide QRS. The escape rhythm may not be sufficient to maintain CO and can progress rapidly to cardiac arrest and death. Mobitz II heart block can occur from ischemia (especially anteroseptal infarcts), endocarditis,

valvular or congenital heart disease, drugs (such as procainamide, disopyramide, and quinidine), or idiopathic progressive cardiac conduction system diseases.

Treatment of clinically significant bradycardia follows the ACLS algorithm outlined in Algorithm 21.2 and aims at maintaining adequate CO. Diagnosis and treatment of reversible causes are paramount (Tables 21.3 and 21.4). Atropine is a first-line transient pharmacologic therapy and is more successful in patients with sinus bradycardia or block within the AV node, rather than block in the more distal His-Purkinje system. Patients who remain clinically unstable require immediate transcutaneous or transvenous pacing. In patients with sinus node dysfunction in which the cause is not reversible, permanent pacing can relieve symptoms. Permanent pacing is typically indicated in second-degree, type 2 AV block, or third-degree AV block. If symptoms of bradycardia are present in second-degree, type 1 AV block, permanent pacing is indicated.

Cardiac Arrest

Cardiac arrest refers to the cessation of a detectable noninvasive blood pressure and pulse. Cardiac arrest can be separated into three main types: (a) pulseless electrical activity (PEA), (b) VT and VF, and (c) asystole. All three fall under the overall heading of pulseless arrest outlined in Algorithm 21.3. Treatment of PEA and asystole are similar and center on identifying reversible causes and employing pharmacologic intervention. VT and VF are treated with immediate electrical defibrillation. The most important aspect of resuscitation remains adequate cardiopulmonary resuscitation (CPR).

Treatment of cardiac arrest in an intensive care unit setting requires a team of nurses and physicians trained in ACLS. Ideally, there should be an established and easily identifiable team leader responsible for continuously evaluating the patient's condition and cardiac rhythm, assimilating incoming data, and giving all orders. In addition, there should be a scribe, recording changes in condition, diagnostic and laboratory data, and therapies delivered. Initial patient evaluation follows the ABCs of cardiac arrest in a coordinated and overlapping

fashion, ensuring adequate airway control, breathing (ie, ventilation), and circulation. In nonintubated patients, an oral airway device should be placed and a bag valve mask should be used to deliver breaths. Intubation is performed when possible. CPR should begin immediately with chest compressions given at a rate of 100 compressions/min at 1.5 to 2 in depth, allowing full chest recoil between compressions. Patients should also be immediately connected to an automated external defibrillator (AED) or a manual defibrillator if an AED is not available. The defibrillator is connected to two pads or paddles placed on the chest wall, with one to the right of the sternum centered on the second intercostal space and the other on the left chest wall centered in the midaxillary line at the fifth intercostal space. IV access should be ensured for the delivery of medications and fluids. Peripheral IV access is initially adequate. However, central IV access should be obtained as soon as possible via the femoral vein, subclavian vein, or internal jugular vein. Endotracheal intubation or central IV access should not interfere with CPR. Pulses are best monitored in the femoral artery, but the carotid arteries may be used. Once airway control is established and the patient is connected to an external defibrillator, the cardiac rhythm should be rapidly analyzed (Algorithm 21.3).

PULSELESS VENTRICULAR TACHYCARDIA AND VENTRICULAR FIBRILLATION

Confirmed VT and VF with hemodynamic collapse should be treated with *immediate* asynchronous defibrillation. Automated AED devices typically deliver escalating biphasic shocks at 200, 300, and 360 J. Manual devices may generate monophasic or biphasic waveforms. If a manual biphasic device is used and the device recommended dose scale is unknown, an initial dose of 200 J should be used, with subsequent shocks at the same or higher doses. If a monophasic device is used, the dose should be 360 J for all shocks. The patient's rhythm, blood pressure, and responsiveness must be continuously monitored with appropriate adjustment of therapy (eg, continuation/discontinuation of CPR, infusion of new medications). If VT/VF persists or recurs after initial treatment, CPR should be resumed immediately after the first shock is given and continued for 2

minutes along with continuous ventilation via a mask airway or endotracheal tube. The rhythm and pulse should be reassessed 2 minutes after the shock is given. Shocks should be repeated if patients remain in pulseless VT/VF and the CPR cycle is repeated. When IV access is established, patients should be concomitantly treated with 1 mg of IV epinephrine every 3 to 5 minutes. After the third shock is given, patients who remain in VF/VT should be considered for amiodarone or lidocaine at the doses shown in Algorithm 21.3. Careful evaluation for a treatable cause should be sought. If a pulse becomes present at any point in treatment, the rhythm should be identified and appropriately treated according to Algorithms 21.1, 21.4, and 21.5.

PULSELESS ELECTRICAL ACTIVITY AND ASYSTOLE

PEA includes numerous pulseless rhythms such as bradyasystolic rhythms, idioventricular rhythms, and ventricular escape rhythms. PEA and asystole are not treated with electrical defibrillation. Treatment centers on well-delivered CPR and pharmacologic intervention as illustrated in Algorithm 21.3. Epinephrine should be given at 1 mg IV every 3 to 5 minutes. If a slow rhythm is seen on the monitor, consider giving atropine 1 mg IV. If IV access is not available, the drugs may be given endotracheally, in which case the dose is generally doubled.

The five H's and five T's listed in Algorithm 21.3 are common conditions that may contribute to cardiac arrest. Airway control and ventilation can correct *hypoxemia.* IV fluids should be given at a wide open rate or via a rapid infuser to correct *hypovolemia.* If *hypoglycemia* is suspected, give 1 ampoule (amp) of 50% dextrose or 1 mg of intramuscular glucagon if IV access is not available. If *hypokalemia* or acidosis (*hydrogen ion*) is suspected, give 1 amp of sodium bicarbonate (50 mEq $NaHCO_3$). *Hypothermia* should be treated as outlined in Chapter 34, Temperature Alterations. Cases of suspected cardiac *tamponade* should be treated with immediate pericardiocentesis (see Chapter 89, ECLS). Suspected *tension* pneumothorax should be treated with rapid decompression by inserting a large-bore catheter (14 or 16 gauge) into the second intercostal space in the midclavicular line, or unilateral or bilaterally inserted thoracostomy tubes (see Chapter 82, Paracentesis). Ischemia from

coronary *thrombosis* should be rapidly identified and treated when patients are stabilized (see Chapter 20, Acute Myocardial Infarction). If pulmonary thrombosis is suspected, fibrinolytics may be beneficial but are not recommended for routine use (see Chapter 16, Pulmonary Embolism).

Cycles of CPR should continue until patients have palpable pulses and a detectable blood pressure or until resuscitation efforts have failed. There is no set period for when to stop resuscitation efforts. The decision to stop CPR is made by the medical team once a full trial at resuscitation has failed and the patient's chances of regaining a pulse and neurologic function are negligible. If patients do regain a pulse, the rhythm on the monitor should be identified and the patient treated accordingly. Blood pressure should be checked and hypotension should be treated with IV vasopressors and IV fluids. An arterial blood gas and other laboratory tests should be checked and abnormalities treated. Consideration of inotropic support or other advanced heart failure therapies should also be made once the patient has been stabilized if cardiogenic shock is associated with the arrest.

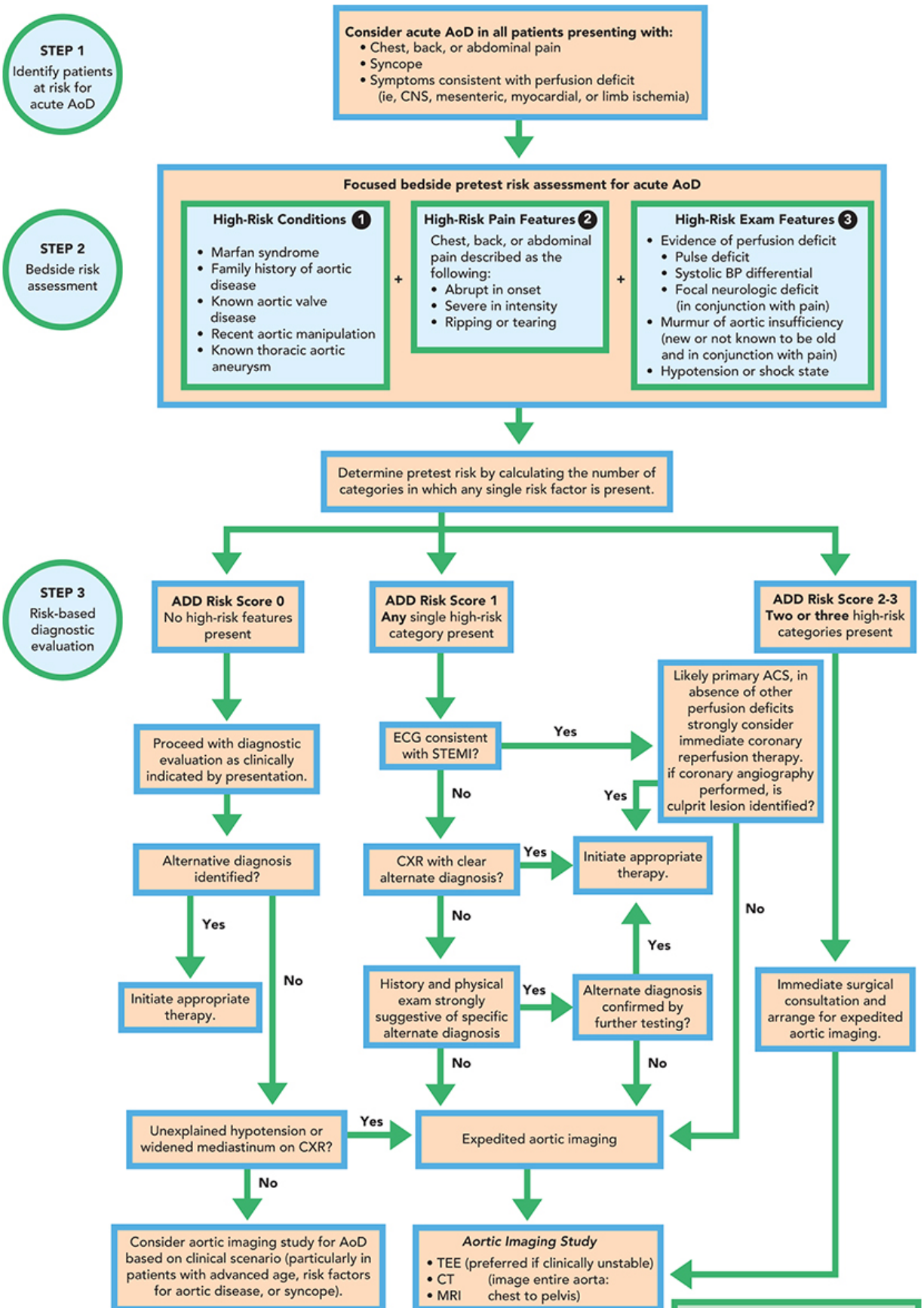
Postresuscitation hypothermia often occurs naturally after cardiac arrest. Active induction of hypothermia has also been evaluated in numerous randomized trials of patients with VF arrest and PEA/asystolic arrest occurring both in- and out-of-hospital. Patients were generally hemodynamically stable but comatose. They were cooled within minutes to hours to between approximately 32 °C and 36 °C, generally with cooling blankets or active cooling systems. There were improved outcomes and metabolic endpoints in patients who were actively cooled. Thus, it is a current American Heart Association 2020 guideline class I recommendation for all adults who do not follow commands after return of spontaneous circulation (ROSC) following an out-of-hospital cardiac arrest with any initial rhythm and all adults who do not follow commands after ROSC following an in-hospital cardiac arrest with an initial shockable or unshockable rhythm meet indication for targeted temperature management (cooling patients between 32 °C and 36 °C for at least 24 hours). Patients with spontaneous hypothermia should not be actively rewarmed. Complications of cooling include coagulopathies and arrhythmias (see Chapter 25, Post Cardiac Arrest Management).

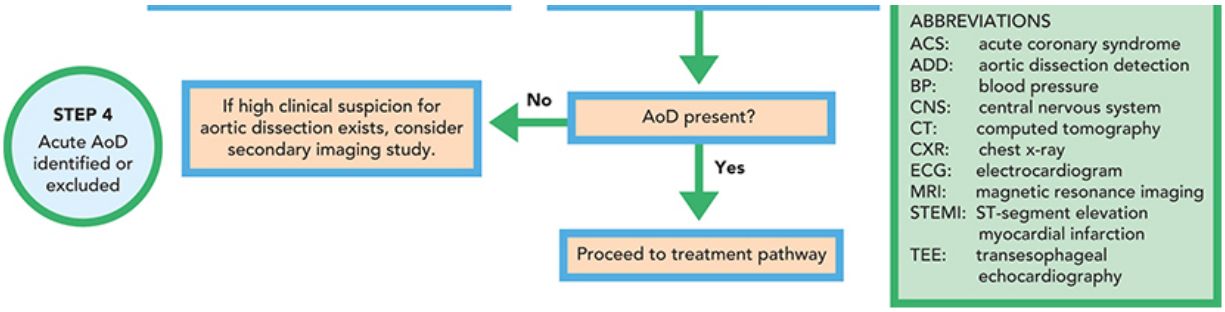
22 Aortic Dissection

Rohan Bhandari and Alan C. Braverman

Aortic dissection is a life-threatening condition that requires prompt diagnosis and treatment. Aortic dissection has an incidence of approximately 3 to 6 per 100,000 people per year. The diagnosis confers substantial morbidity and mortality, with a mortality rate of upward of 0.5 to 1% per hour within the first several hours. An algorithm for the immediate approach to the patient with aortic dissection is presented in Algorithms 22.1 and 22.2.

ALGORITHM 22.1 Evaluation of Aortic Dissection

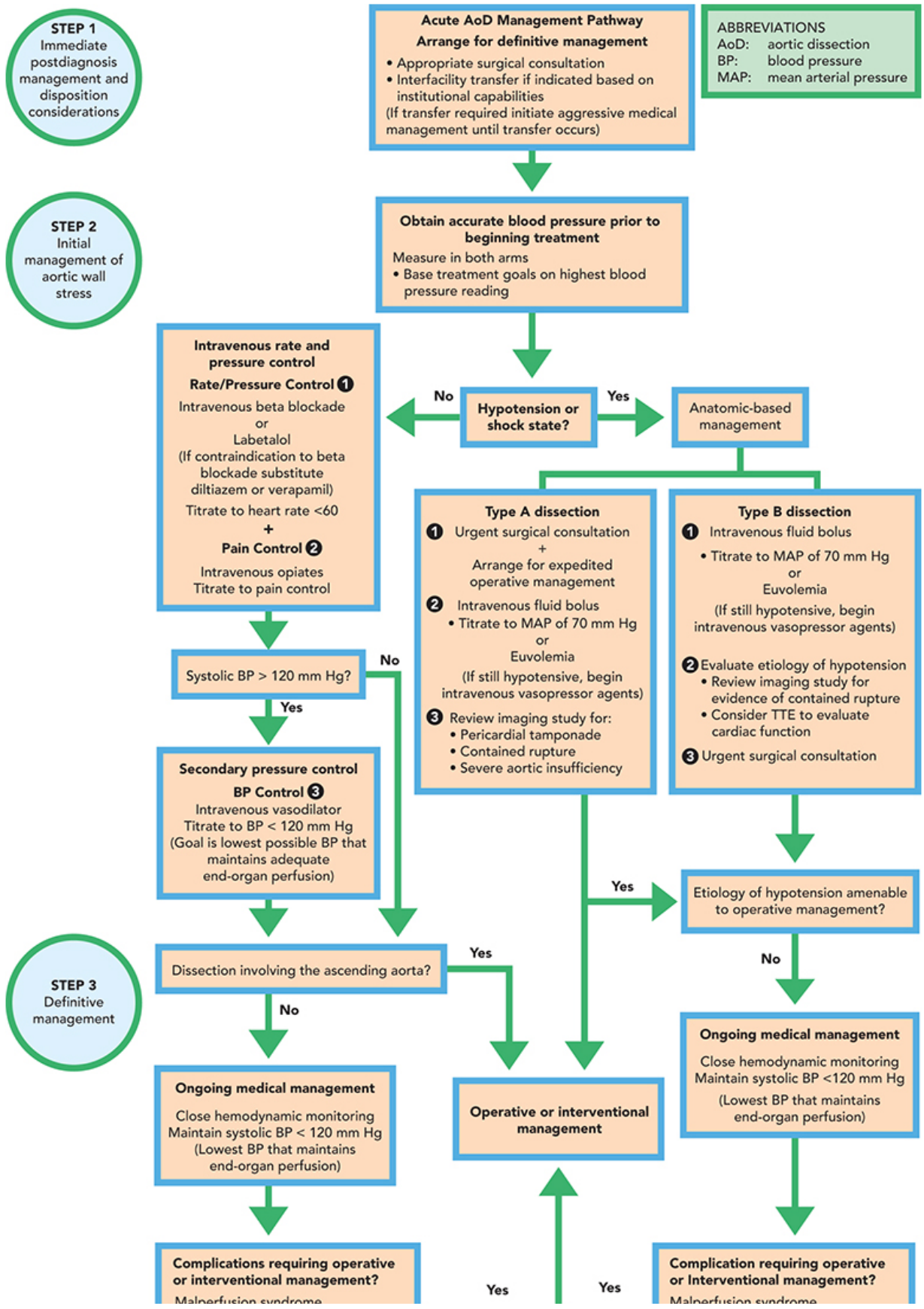

STEP 1
Identify patients at risk for acute AoD
Consider acute AoD in all patients presenting with:
• Chest, back, or abdominal pain
• Syncope
• Symptoms consistent with perfusion deficit (ie, CNS, mesenteric, myocardial, or limb ischemia)
STEP 2
Bedside risk assessment
Focused bedside pretest risk assessment for acute AoD
High-Risk Conditions 1
• Marfan syndrome
• Family history of aortic disease
• Known aortic valve disease
• Recent aortic manipulation
• Known thoracic aortic aneurysm
+
High-Risk Pain Features 2
Chest, back, or abdominal pain described as the following:
• Abrupt in onset
• Severe in intensity
• Ripping or tearing
+
High-Risk Exam Features 3
• Evidence of perfusion deficit
• Pulse deficit
• Systolic BP differential
• Focal neurologic deficit (in conjunction with pain)
• Murmur of aortic insufficiency (new or not known to be old and in conjunction with pain)
• Hypotension or shock state
Determine pretest risk by calculating the number of categories in which any single risk factor is present.
STEP 3
Risk-based diagnostic evaluation
ADD Risk Score 0
No high-risk features present
ADD Risk Score 1
Any single high-risk category present
ADD Risk Score 2-3
Two or three high-risk categories present
Proceed with diagnostic evaluation as clinically indicated by presentation.
ECG consistent with STEMI?
Yes
Likely primary ACS, in absence of other perfusion deficits strongly consider immediate coronary reperfusion therapy.
if coronary angiography performed, is culprit lesion identified?
Yes
No
Alternative diagnosis identified?
CXR with clear alternate diagnosis?
Yes
Initiate appropriate therapy.
Yes
No
No
Yes
Initiate appropriate therapy.
No
History and physical exam strongly suggestive of specific alternate diagnosis
Yes
Alternate diagnosis confirmed by further testing?
Immediate surgical consultation and arrange for expedited aortic imaging.
No
No
Unexplained hypotension or widened mediastinum on CXR?
Yes
Expedited aortic imaging
No
Consider aortic imaging study for AoD based on clinical scenario (particularly in patients with advanced age, risk factors for aortic disease, or syncope).
Aortic Imaging Study
• TEE (preferred if clinically unstable)
• CT (image entire aorta: chest to pelvis)
• MRI

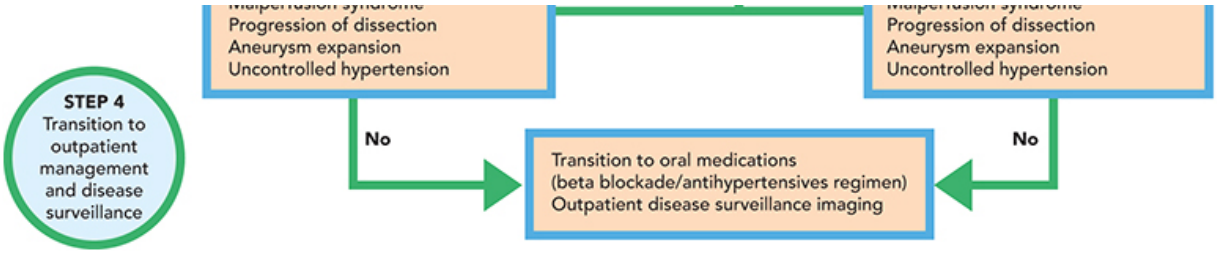


Evaluation pathway for aortic dissection (AoD).

Reproduced with permission from Rogers AM, Hermann LK, Booher AM, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the International Registry of Acute Aortic Dissection. *Circulation*. 2011;123(20):2213-2218.

ALGORITHM 22.2 Management of Aortic Dissection

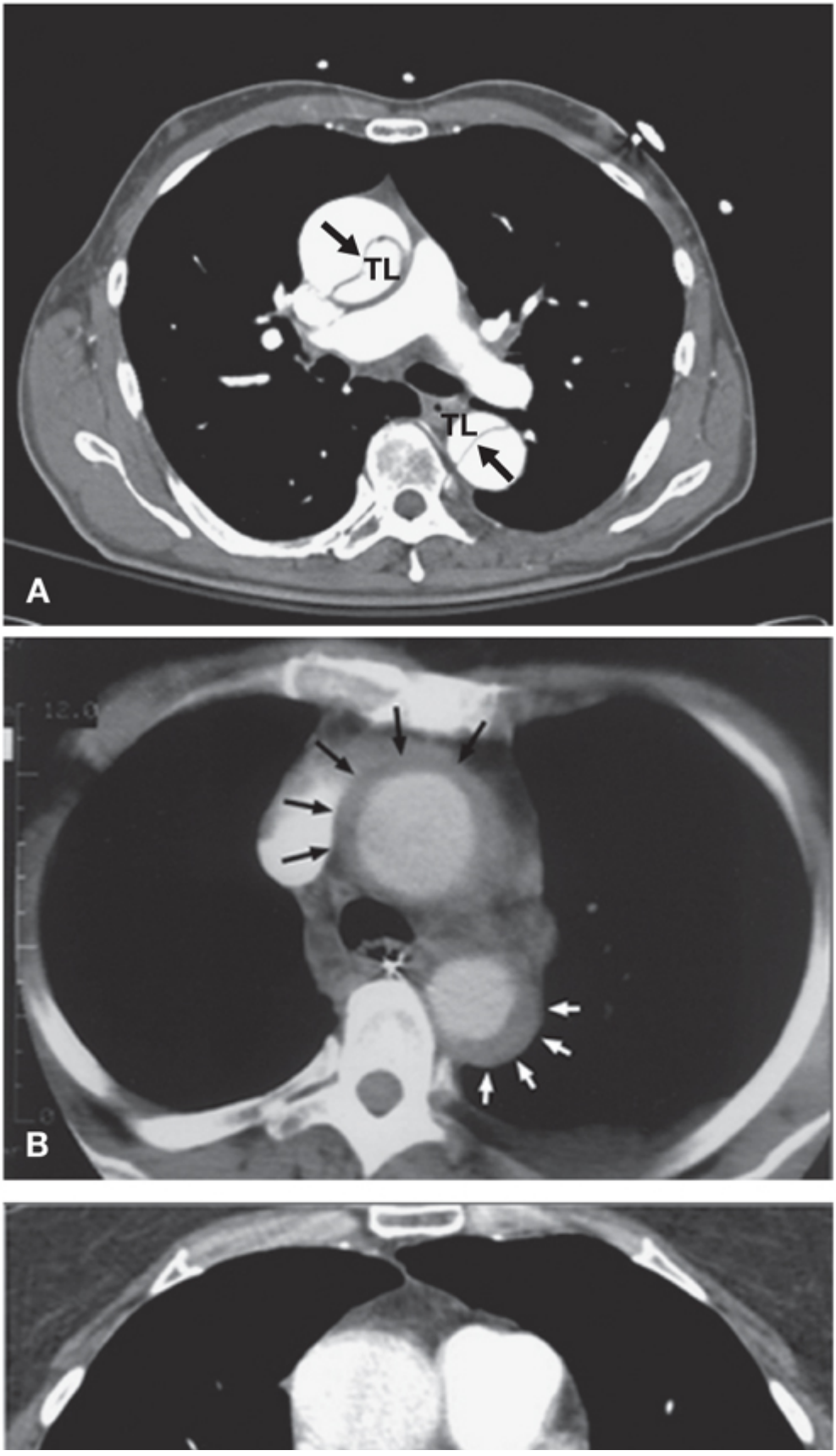

STEP 1
Immediate postdiagnosis management and disposition considerations
STEP 2
Initial management of aortic wall stress
STEP 3
Definitive management
Acute AoD Management Pathway
Arrange for definitive management
• Appropriate surgical consultation
• Interfacility transfer if indicated based on institutional capabilities
(If transfer required initiate aggressive medical management until transfer occurs)
ABBREVIATIONS
AoD: aortic dissection
BP: blood pressure
MAP: mean arterial pressure
Obtain accurate blood pressure prior to beginning treatment
Measure in both arms
• Base treatment goals on highest blood pressure reading
Hypotension or shock state?
No
Yes
Anatomic-based management
Intravenous rate and pressure control
Rate/Pressure Control ❶
Intravenous beta blockade
or
Labetalol
(If contraindication to beta blockade substitute diltiazem or verapamil)
Titrate to heart rate <60
+
Pain Control ❷
Intravenous opiates
Titrate to pain control
Systolic BP > 120 mm Hg?
No
Yes
Secondary pressure control
BP Control ❸
Intravenous vasodilator
Titrate to BP < 120 mm Hg
(Goal is lowest possible BP that maintains adequate end-organ perfusion)
Type A dissection
❶ Urgent surgical consultation
+
Arrange for expedited operative management
❷ Intravenous fluid bolus
• Titrate to MAP of 70 mm Hg
or
Euvolemia
(If still hypotensive, begin intravenous vasopressor agents)
❸ Review imaging study for:
• Pericardial tamponade
• Contained rupture
• Severe aortic insufficiency
Type B dissection
❶ Intravenous fluid bolus
• Titrate to MAP of 70 mm Hg
or
Euvolemia
(If still hypotensive, begin intravenous vasopressor agents)
❷ Evaluate etiology of hypotension
• Review imaging study for evidence of contained rupture
• Consider TTE to evaluate cardiac function
❸ Urgent surgical consultation
Dissection involving the ascending aorta?
Yes
No
Etiology of hypotension amenable to operative management?
Yes
No
Ongoing medical management
Close hemodynamic monitoring
Maintain systolic BP < 120 mm Hg
(Lowest BP that maintains end-organ perfusion)
Operative or interventional management
Ongoing medical management
Close hemodynamic monitoring
Maintain systolic BP <120 mm Hg
(Lowest BP that maintains end-organ perfusion)
Complications requiring operative or interventional management?
Malperfusion syndrome
Yes
Yes
Complication requiring operative or Interventional management?
Malperfusion syndrome



Management pathway for acute aortic dissection (AoD).
Reproduced with permission from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol*. 2010;55(14):e27-e129.

Acute aortic syndromes include classic aortic dissection, aortic intramural hematoma (IMH), and penetrating atherosclerotic aortic ulcer (PAU). “Classic” aortic dissection results from a tear in the intimal layer of the aorta, allowing blood to enter the media and propagate in an anterograde or retrograde direction, resulting in a second or “false” lumen (Figure 22.1A). Reentry tears may occur and allow reconnection with the true lumen. Aortic IMH accounts for 10% to 20% of aortic syndromes (Figure 22.1B). In aortic IMH, hemorrhage occurs in the medial layer without a visible intimal tear or communication with the aortic lumen. Aortic IMH is generally treated similarly to aortic dissection, with emergency surgery for type A IMH and medical therapy for type B IMH. IMH may demonstrate focal intimal defects, progress to classical dissection, lead to aneurysmal dilation or spontaneously resolve. PAU arises when an atherosclerotic lesion of the aorta develops ulceration that penetrates the intimal and medial layers (Figure 22.1C), which may lead to a pseudoaneurysm that can dissect or rupture and most commonly occurs in the descending and abdominal aorta. Once an aortic dissection occurs, shear stress stemming from the rate of

change in pressure (dP/dt) and mean arterial blood pressure contribute to the propagation of the tear.


TL
TL
A
B

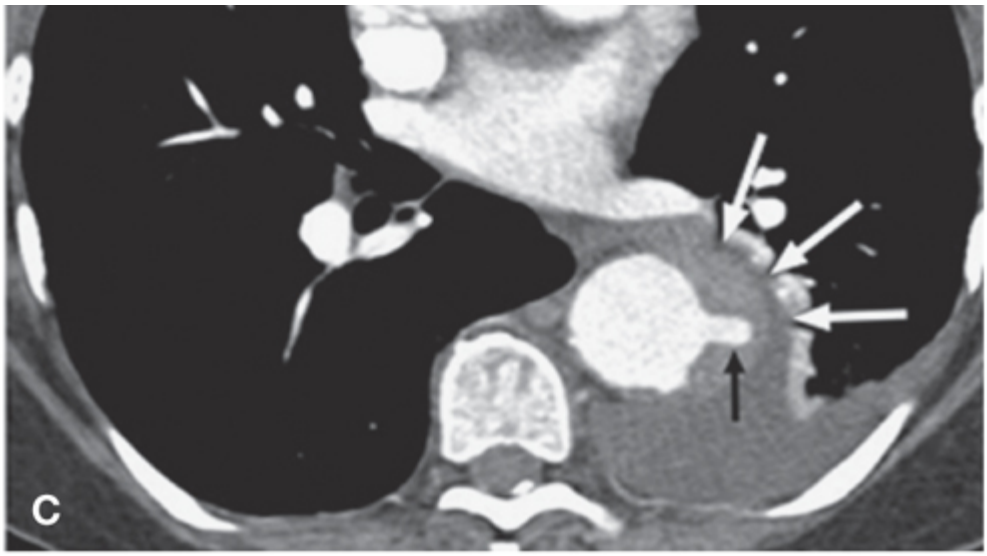


FIGURE 22.1 **Types of acute aortic syndromes**. **A:** "Classic" type A aortic dissection. *Black arrows* indicate intimal flaps. The true lumen (TL) is usually the smaller lumen. **B:** Type A intramural hematoma (IMH) of the aorta. *Black arrows* indicate circumferential IMH in the ascending aorta and *white arrows* denote crescentic IMH in descending aorta. **C:** Penetrating atherosclerotic ulcer (PAU) of the aorta (*black arrow*). *White arrows* point to associated intramural hematoma. (Reproduced with permission from Braverman AC. Diseases of the aorta. In: Bonow RO, Mann DL, Zipes DP, et al., eds. *Braunwald's Heart Disease*. 10th ed. Elsevier; 2015:1277-1311.)

Several conditions predispose the aorta to dissection, due to either primary abnormalities in the composition of the aortic wall or excess aortic wall shear stress (Table 22.1). Approximately 75% of patients with aortic dissection have hypertension. Patients with genetic aortopathies, including syndromic heritable thoracic aortic diseases (HTAD) (Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome), and nonsyndromic HTAD (also known as familial thoracic aortic aneurysms, which are due to pathogenic mutations in *ACTA2, MYH11, MYLK, PRKG1,* and others) are at risk for aortic dissection. Congenital disorders including Turner syndrome and bicuspid aortic valve with aortic root and/or ascending aortic aneurysm are at risk for aortic dissection. Pheochromocytoma, cocaine- or methamphetamine-induced hypertension; inflammatory

aortitis such as giant cell arteritis; and direct trauma from aortic instrumentation or aortic surgery can disrupt the aortic wall. Once the intima becomes injured, it is vulnerable to shear stress and may progress further to dissection or rupture.

TABLE 22.1 Risk Factors for Aortic Dissection

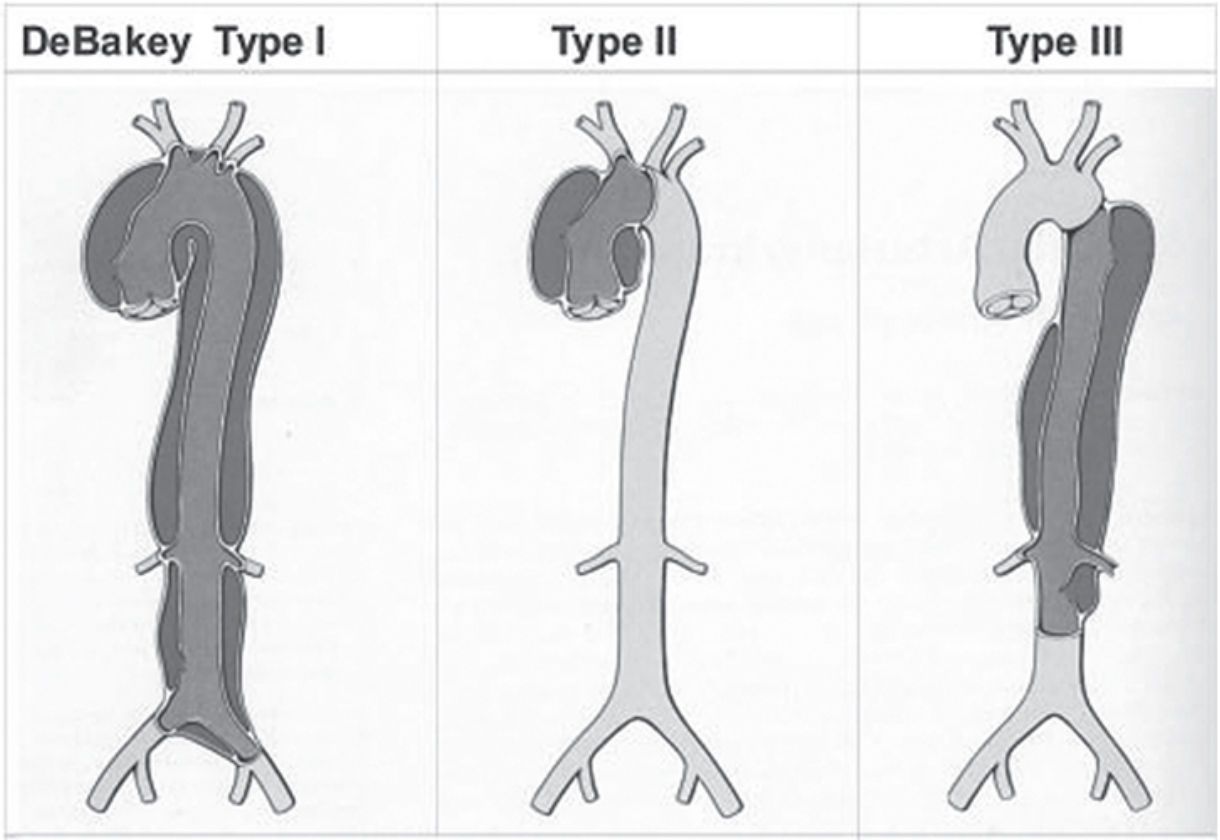
Traditional CVD risk factors	Hypertension Atherosclerosis/penetrating atherosclerotic ulcer (PAU) Smoking
Syndromic HTAD	Marfan syndrome (*FBN1*) Loeys-Dietz syndrome (*TGFBR1, TGFBR2, SMAD3, TGFB2, TGFB3*) Vascular Ehlers-Danlos (*COL3A1*)
Nonsyndromic HTAD	Related to pathogenic variants in *ACTA2, MYH11, MYLK, PRKG1*, and other genes Familial thoracic aortic aneurysm and dissection (without gene discovered)
Congenital conditions	Bicuspid aortic valve with thoracic aortic aneurysm Turner syndrome Aortic coarctation
Inflammatory aortitis	Giant cell arteritis Takayasu arteritis Behçet disease Syphilitic aortitis IgG-4-related aortitis
Aortic manipulation	Aortic valve surgery Transcatheter aortic valve replacement (TAVR) TEVAR/EVAR Cardiac catheterization/aortography Intra-aortic balloon pump implantation
Other	Cocaine and methamphetamine use Pheochromocytoma Pregnancy[a] Trauma

CVD, cardiovascular disease; EVAR, endovascular aortic repair; HTAD, heritable thoracic aortic disease; TEVAR, transcatheter endovascular aortic repair.

[a]With concomitant aortopathy.

Reproduced with permission from Braverman AC, Schermerhorn. Diseases of the aorta. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, Solomon SD, eds. *Braunwald's Heart Disease*. 12th ed. Elsevier; 2022:806-836.

There are several anatomic classification systems of aortic dissection, and involvement of the ascending aorta is the defining characteristic (Figure 22.2). DeBakey types I and II and Stanford type A dissections involve the ascending aorta, whereas DeBakey type III or Stanford type B dissections do not. The location of the acute dissection is important because decisions regarding surgical or initial medical management are dependent on the location of the dissection. Acute dissection of the ascending aorta (Stanford type A, DeBakey types I and II) requires immediate surgical repair, while initially uncomplicated dissection involving the descending aorta (Stanford type B or DeBakey type III) without high-risk features is treated medically. Aortic dissection involves the ascending aorta nearly twice as frequently as the descending aorta. The chronicity of aortic dissection is defined by the duration of symptoms at the time of presentation. Importantly, serious complications such as aortic rupture and branch vessel occlusion are more likely to occur in the acute phase of dissection rather than the chronic phase. A classification system from the International Registry of Acute Aortic Dissection (IRAD) stratifies aortic dissection into four temporal groups based on the risk of mortality during each time period and includes hyperacute (0-24 hours), acute (2-7 days), subacute (8-30 days), and chronic phases (>30 days) (Figure 22.3).



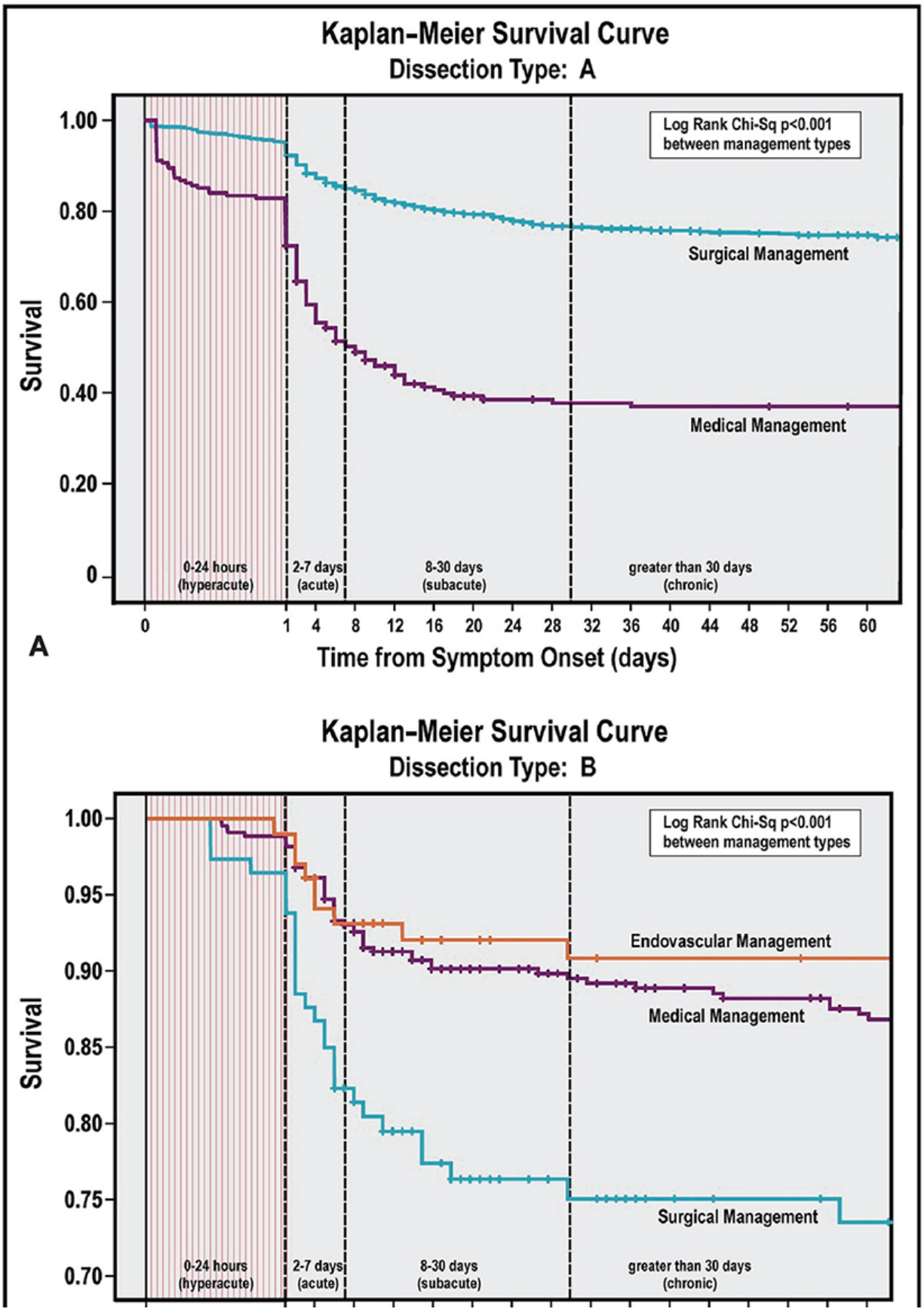
DeBakey

Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally
Type II	Originates in and is confined to the ascending aorta
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely, retrograde into the aortic arch and ascending aorta

Stanford

Type A	All dissections involving the ascending aorta, regardless of the site of origin
Type B	All dissections not involving the ascending aorta

FIGURE 22.2 **Classification systems of aortic dissection: DeBakey and Stanford**. (Reproduced with permission from Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management. Part I: from etiology to diagnostic strategies. *Circulation*. 2003;108(5):628-635.)


Kaplan-Meier Survival Curve
Dissection Type: A
Log Rank Chi-Sq p<0.001
between management types
Surgical Management
Medical Management
Survival
1.00
0.80
0.60
0.40
0.20
0
0-24 hours
(hyperacute)
2-7 days
(acute)
8-30 days
(subacute)
greater than 30 days
(chronic)
0
1
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
Time from Symptom Onset (days)
A
Kaplan-Meier Survival Curve
Dissection Type: B
Log Rank Chi-Sq p<0.001
between management types
Endovascular Management
Medical Management
Surgical Management
Survival
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0-24 hours
(hyperacute)
2-7 days
(acute)
8-30 days
(subacute)
greater than 30 days
(chronic)

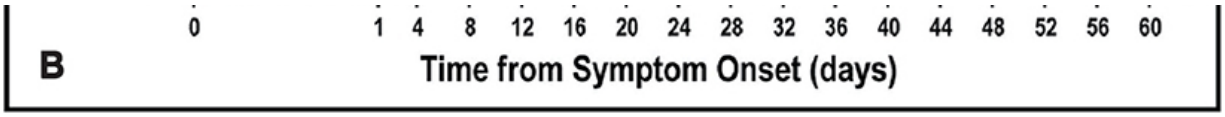


FIGURE 22.3 **Survival curves for acute aortic dissection by type and management**. **A:** Kaplan-Meier survival curve for type A dissection stratified by treatment type. **B:** Kaplan-Meier survival curve for type B dissection stratified by treatment type. (Reproduced with permission from Booher AM, Isselbacher EM, Nienaber CA, et al. The IRAD classification system for characterizing survival after aortic dissection. *Am J Med*. 2013;126(8):730.e19-730.e7.3E24.)

The clinical presentation of aortic dissection may be quite variable and mimic presentations of more common syndromes (myocardial infarction, pulmonary embolism, heart failure, syncope, limb ischemia); therefore, a high index of clinical suspicion is critical for the rapid diagnosis of aortic dissection. “Think Aorta” is an important catchphrase when approaching the individual with signs and symptoms of aortic dissection, especially unexplained acute chest pain, neck pain, back pain, and/or syncope. The Aortic Dissection Detection Risk Score (ADD-RS) incorporates high-risk conditions, high-risk symptoms and pain features, and high-risk examination features to provide a bedside assessment tool that aids in risk-stratifying patients with presentations concerning aortic dissection. The ADD-RS is scored between 0 and 3, with 0 points indicating low risk, 1 point suggestive of moderate risk, and 2 or 3 points concerning for high risk or pretest probability of aortic dissection. The key features and scoring system for the ADD-RS are incorporated into Algorithm 22.1 and listed in Table 22.2. Individuals with one or more of these features and unexplained signs or symptoms that could represent aortic dissection should have further evaluation. In contrast to the crescendo discomfort of angina pectoris, the pain of acute dissection is often maximal at its onset, sudden, sharp, severe, and located in the chest and/or back and neck. Syncope may accompany type A dissection and is usually a result of cardiac tamponade, aortic rupture, or cerebrovascular involvement of the dissection. In addition to the dissection itself, presenting symptoms

may be related to malperfusion of end-organ systems. Physical examination should include obtaining pulses in all extremities and blood pressure in both arms, as there may be pulse or blood pressure deficits. Cardiac auscultation may reveal an aortic regurgitation murmur. While important when present, pulse deficits are observed in only ~25% of patients and an aortic regurgitation murmur in less than half. Thus, the absence of these physical examination features is not sufficient to exclude aortic dissection.

TABLE 22.2 The Aortic Dissection Detection Risk Score (ADD-RS)

High-Risk Conditions	High-Risk Symptoms and Pain Characteristics	High-Risk Examination Features
Marfan syndrome or other aortopathy connective tissue disorder	Abrupt onset	Pulse deficit or systolic blood pressure differential
Family history of aortic disease	Severe in intensity	Focal neurologic deficit (with pain)
Known aortic valve disease	Ripping or tearing in quality	New murmur of aortic regurgitation with pain
Recent aortic manipulation		Hypotension or shock state
Known thoracic aortic aneurysm		

For each risk category, 1 point is assigned if ≥1 risk factor is present. An ADD-RS of 0 point is low risk; 1 point is moderate risk; and 2 to 3 points is high risk.
Reproduced with permission from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular

Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *J Am Coll Cardiol.* 2010;55(14):e27-e129.

The significant morbidity and mortality associated with aortic dissection are largely attributed to malperfusion with end-organ damage and aortic rupture (Table 22.3). Organ systems may be compromised by intermittent compression of branch vessels due to an expanding false lumen (dynamic malperfusion) or direct extension of dissection into the vessel that may lead to thrombosis (static malperfusion) (Figure 22.4). In type A dissection, cardiac tamponade, aortic regurgitation leading to heart failure, aortic rupture, and/or myocardial infarction from coronary artery involvement may lead to hemodynamic shock and death. When cardiac tamponade complicates type A dissection, emergent surgery is recommended. Poor outcomes have been reported with pericardiocentesis owing to lowering of the intrapericardial pressure, which may cause further bleeding and hemodynamic collapse. However, if emergency surgery cannot be performed expediently in the setting of refractory shock, limited pericardiocentesis to remove just enough pericardial blood to improve blood pressure can be lifesaving. Neurologic sequelae including syncope, altered mental status, stroke, and deficits in motor function or sensory loss may result from cerebral or spinal cord hypoperfusion from an acute dissection involving the carotid, vertebral, or spinal arteries. Mesenteric, limb, or renal ischemia may occur due to branch vessel occlusion. Hence, the clinician must remain vigilant in monitoring for evidence of end-organ malperfusion and potential associated clinical symptoms in the patient with known aortic dissection.

TABLE 22.3 Complications of Aortic Dissection

Cardiovascular	Aortic regurgitation
Peripheral vascular	Congestive heart failure
	Myocardial ischemia or infarction
	Cardiac tamponade

	Cardiac arrest Syncope Pericarditis Upper- or lower extremity limb ischemia
Pulmonary	Pleural effusion Hemothorax Hemoptysis
Renal	Renovascular hypertension Renal ischemia or infarction Acute renal failure
Neurologic	Transient ischemic attack or stroke Paraparesis or paraplegia Encephalopathy or coma Spinal cord syndrome Ischemic neuropathy
Gastrointestinal	Mesenteric ischemia or infarction Ileus/abdominal pain Pancreatitis Ischemic hepatitis Hematemesis
Systemic	Fever

Reproduced with permission from Braverman AC, Schermerhorn. Diseases of the aorta. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, Solomon SD, eds. *Braunwald's Heart Disease*. 12th ed. Elsevier; 2022, 806-836.

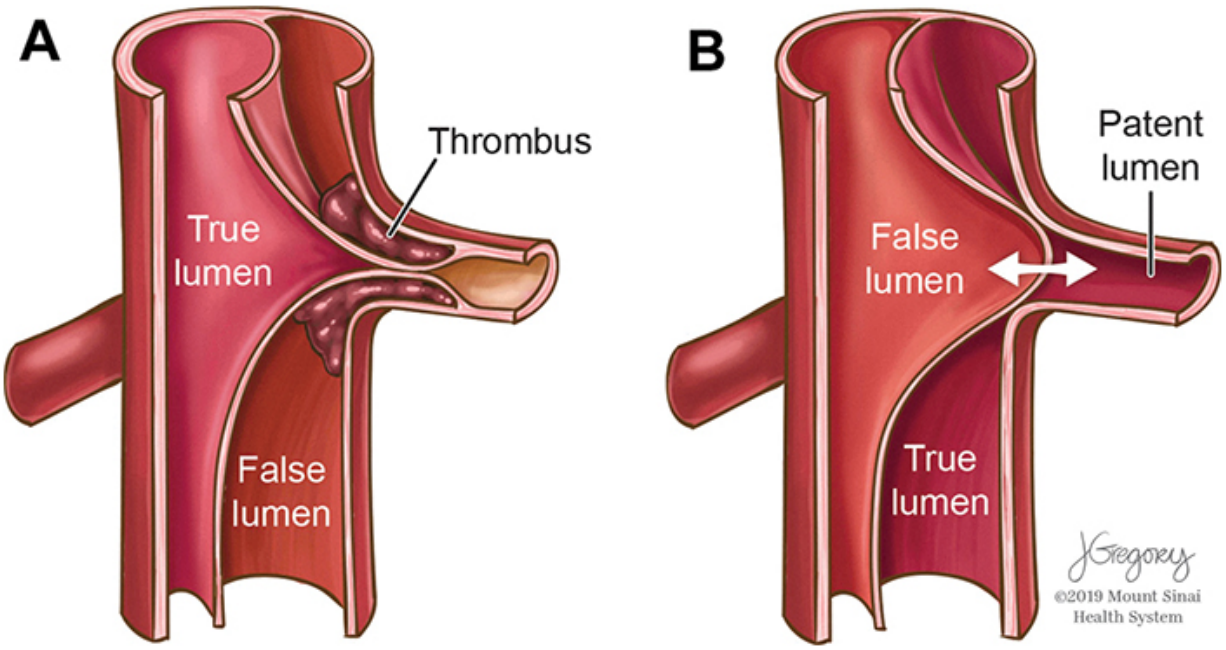


FIGURE 22.4 **Static and dynamic obstruction in malperfusion syndrome**. This figure depicts two causes of malperfusion syndrome: **(A)** static and **(B)** dynamic obstruction. Static obstruction is the result of any fixed obstruction and the most common cause, dissection of the branch vessel and thrombosis of the false lumen, is shown here. Dynamic obstruction is the more common cause of malperfusion syndrome and occurs when the branch vessel ostium is intermittently blocked by the dissection flap. (Reproduced with permission from: Tadros RO, Tang GHL, Barnes HJ, et al. Optimal treatment of uncomplicated type B aortic dissection: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74(11):1494-1504.)

Standard imaging and laboratory tests may assist in the evaluation and diagnosis of aortic dissection. The chest x-ray (CXR) may demonstrate a widened mediastinum or abnormal aortic contour. Pleural effusion may represent hemothorax, and separation of the intimal calcification from the outer aortic soft tissue border by more than 10 mm, or the radiologic “calcium sign,” may indicate an intimal flap. Because 20% of CXRs do not demonstrate abnormal findings, a normal CXR cannot exclude aortic dissection. The electrocardiogram (ECG) is often nonspecific, although evidence of coronary ischemia or injury may be present when the dissection involves a coronary

artery. The D-dimer, a degradation product of cross-linked fibrin, is usually markedly elevated in acute aortic dissection. In the first 24 hours from symptom onset, a D-dimer of <500 ng/mL has a negative predictive value of 95%. Importantly in IMH or PAU, the D-dimer may not be elevated. However, in the setting of a high clinical index of suspicion, a normal D-dimer should not rule out an acute aortic syndrome. Other important laboratory tests to obtain to evaluate for complications of aortic dissection include a complete blood count, comprehensive metabolic profile, lactic acid, troponin, lactate dehydrogenase, and creatine kinase levels.

Due to the life-threatening nature of aortic dissection, immediate diagnostic confirmation and definition of the extent of the dissection is imperative. The choice of imaging should be made on the basis of patient hemodynamic stability and operator availability. The sensitivity and specificity of the most commonly used imaging modalities and their relative advantages and disadvantages are shown in Table 22.4. ECG-gated contrast CT is widely and rapidly available and is the most commonly used initial imaging modality to diagnose and evaluate for complications of acute dissection. CT scans provide outstanding imaging of the entire aorta and branch vessels, as well as providing the ability to create three-dimensional reconstructions that can aid in treatment planning. Other less commonly employed imaging strategies for the initial diagnosis of an acute aortic dissection include transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), and magnetic resonance angiography (MRA). Given the lower sensitivity of TTE, a normal TTE cannot exclude dissection. TEE requires an experienced operator and esophageal intubation to perform the procedure; however, it can be performed at the bedside; does not require contrast dye; and visualizes the aortic valve, aortic root, and pericardium well. Despite its high sensitivity and specificity, MRA is not typically the test of first choice in acute aortic dissection, due to the longer image acquisition time and lesser availability on an emergent basis.

TABLE 22.4 Comparison of Diagnostic Imaging Modalities

Test	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
TTE[a]	85-90	93-96	• Rapidly available • Can be done at the bedside	• Poor sensitivity for type B aortic dissection • May be limited by poor acoustic windows
TEE	98-99	95	• Excellent evaluation of aortic root, descending thoracic aorta, aortic valve, and pericardium • Can be done at the bedside	• Requires esophageal intubation (which may affect hemodynamics) • Limited to thoracic aorta
CT[b]	98-100	98-100	• Widely and rapidly available • Superior imaging of the entire aorta, heart, and branch vessels, and detection of complications such as rupture or hemopericardium	• Ionizing radiation and nephrotoxic iodinated contrast required

Test	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
MRI[c]	>98	>98	• Superior accuracy, sensitivity, and specificity for all types of dissection	• Limited availability • Time-consuming procedure • More difficult to monitor patients during the test

CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

[a]Sensitivity and specificity for the use of TTE in identifying type A dissection; the ability of TTE to identify type B aortic dissection is much lower.

[b]With iodinated contrast.

[c]With gadolinium-based contrast.

When aortic dissection is suspected, immediate initiation of beta-blocker therapy (unless contraindicated) to reduce shear stress is paramount while simultaneously pursuing confirmation of the diagnosis (Table 22.5). Intravenous beta-blocker therapy titrated to achieve a systolic blood pressure (SBP) of less than 120 mm Hg and a target heart rate below 60 to 70 beats/min is recommended. The target SBP should be as low as possible (<120 mm Hg) without compromising end-organ perfusion. If the SBP remains elevated despite the initiation of beta-blocker therapy, then additional agents, such as intravenous nicardipine or sodium nitroprusside, should be added. Importantly, vasodilator therapy should not be initiated prior to starting beta-blocker therapy, as vasodilators may induce reflex tachycardia, thereby increasing dP/dt and potentially promoting further extension of the dissection. Opioids, if needed, for pain control are an important adjunct to aid in achieving blood pressure goals. Once the patient is stabilized and heart rate and blood

pressure goals are met, the patient can be transitioned to oral beta-blocker and additional antihypertensive therapy.

TABLE 22.5 Pharmacologic Therapy for Acute Aortic Syndromes[a]

1. Intravenous beta-blocker (preferred initial therapy)[b]
   - **Esmolol:** Intravenous (IV) Bolus: 250-500 mcg/kg IV, then continuous IV infusion: at 50-100 mcg/kg/min, titrated to effect. Short half-life allows rapid titration.
   - **Labetalol:** IV Bolus: 20 mg over 2 min, then IV push: 20-80 mg IV every 10 min until adequate response (maximum dose 300 mg). Start continuous IV infusion: at 0.5-2 mg/min and titrate to response.

2. Intravenous vasodilator (use after initiation of beta-blocker therapy)
   - **Clevidipine**: Start continuous IV infusion: at 1-2 mg/h; can double dose up to a maximum dose of 16-32 mg/h
   - **Nicardipine:** Start continuous IV infusion: at 5 mg/h, then increase by 2.5 mg/h every 5-15 min up to a maximum of 15 mg/h. For rapidly titrated patients, consider reduction to 3 mg/h after adequate BP response is achieved.
   - **Sodium nitroprusside**: Start continuous IV infusion: at 0.3-0.5 mcg/kg/min, titrate by 0.5 mcg/kg/min every few minutes to desired effect; maximum dose of 10 mcg/kg/min (some recommend a maximum dose of 2 mcg/kg/min to avoid toxicity). Caution: Thiocyanate toxicity may occur with prolonged infusions or in patients with renal impairment.
   - **Enalaprilat:** IV Bolus: 0.625-1.25 mg/dose over 5 min, then increase by 0.625-1.25 mg/dose every 6 h to a maximum of 5 mg/dose every 6 h (titrated to effect).
   - **Fenoldopam**: Start continuous IV infusion at 0.1 mcg/kg/min, then titrate up to a maximum of 1.6 mcg/kg/min.

[a]Goal of therapy is heart rate (HR) of less than 60-70 beats/min and systolic blood pressure of less than 120 mm Hg or as low as possible without compromising end-organ perfusion.

[b]If beta-blockers are contraindicated, consider the use of diltiazem: 0.25 mg/kg IV over 2 minutes, then continuous IV infusion at 5-15 mg/h, titrated to effect.

Reproduced with permission from Braverman AC, Schermerhorn. Diseases of the aorta. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, Solomon SD, eds. *Braunwald's Heart Disease*. 12th ed. Elsevier; 2022:806-836.

Emergent surgery is indicated in patients with type A dissection, as medical therapy alone is associated with a high risk of morbidity and mortality in these patients (Figure 22.3). Thoracic endovascular repair (TEVAR) is recommended for complicated type B dissection in the setting of aortic rupture, malperfusion syndromes, rapidly expanding aortic dimensions, refractory pain, uncontrolled hypertension, and is considered for patients with high-risk imaging features. Endovascular stent grafting covers the intimal tear, decompresses the false channel, and improves perfusion to the true lumen and its branches (Figure 22.5). Open surgery for complicated type B dissection carries a high risk and is reserved for complications that are unable to be managed by TEVAR. Randomized trials are being planned to evaluate the use of TEVAR in uncomplicated type B dissection; however, at present, uncomplicated type B aortic dissections are initially treated medically. Figure 22.6 summarizes medical and interventional/surgical approaches to the management of complicated and uncomplicated type B aortic dissections.

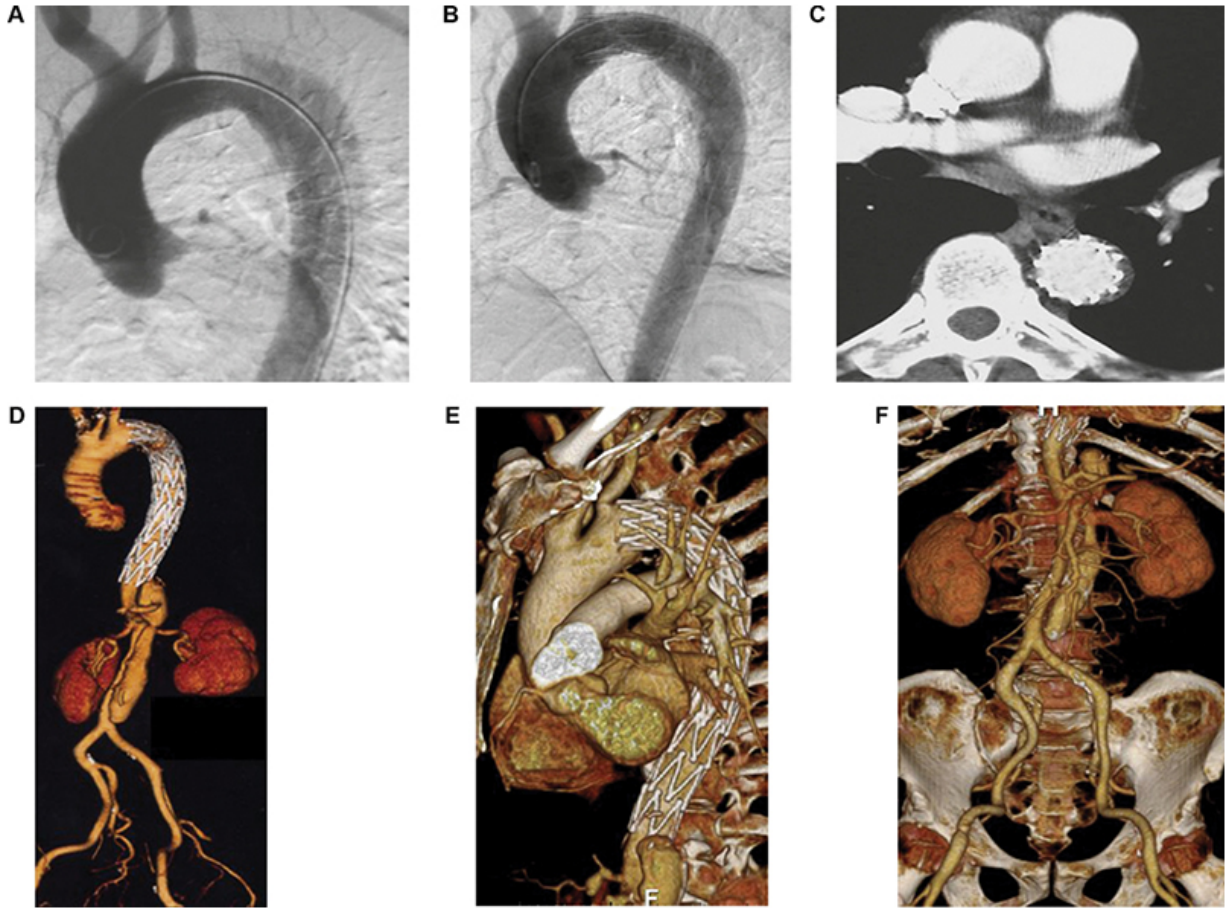


FIGURE 22.5 **Long-term follow-up of TEVAR for management of type B aortic dissection**. **A:** Left anterior oblique projection from thoracic aortogram documents type B aortic dissection in a 49-year-old man with acute abdominal and back pain. **B:** Repeat aortogram post stent-graft placement without antegrade opacification of the false lumen. **C:** Axial CT image at mid-thoracic level 20 months post TEVAR shows stent graft within the true lumen and complete thrombosis of the false lumen that appears now as only a crescentic remnant along the posterolateral aortic border. **D:** Three-dimensional reconstruction CT dataset obtained 8 years after TEVAR details stable appearance to thoracic aorta and residual patency of the abdominal false lumen without interval enlargement. **E** and **F:** Rendering of thoracic and abdominal CT scan performed 22 years post original TEVAR depicts stable appearance without interval disease progression. CT, computed tomography; TEVAR, thoracic endovascular aortic repair. (Reproduced with permission from Thakkar D, Dake MD. Management of type B aortic dissections: treatment of acute dissections and acute

complications from chronic dissections. *Tech Vasc Interv Radiol*. 2018;21:124-130.)

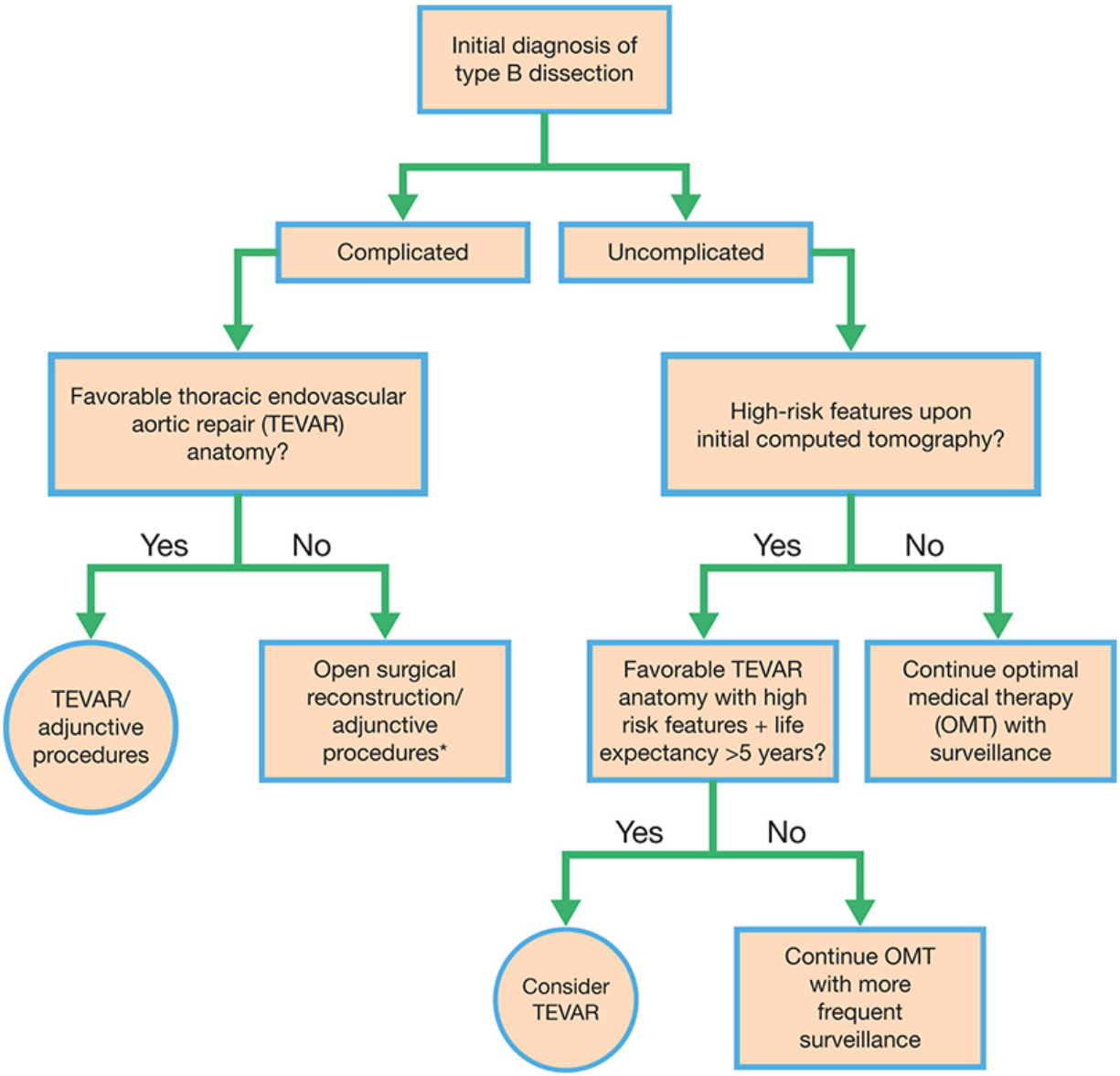


FIGURE 22.6 **Management algorithm for acute type B aortic dissection**. Adjunctive procedures are, for example, endovascular stenting, surgical revascularization, coil embolization, and selective branch vessel stenting. High-risk features include primary entry tear diameter greater than 10 mm, initial aortic diameter greater than 40 mm, false lumen diameter greater than 22 mm, partially thrombosed false lumen, and saccular false lumen formation. OMT, optimal medical therapy; TEVAR, thoracic endovascular aortic repair. (Reproduced with permission from Tadros RO, Tang

GHL, Barnes HJ, et al. Optimal treatment of uncomplicated type B aortic dissection: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:1494-1504.)

Following acute aortic dissection, screening for underlying genetic aortic disease, evaluating family members, and providing education about lifestyle modification are all necessary. Up to 20% of nonsyndromic patients with thoracic aortic dissection will have a first-degree relative with aortic dilation/disease. Physical examination with particular attention to features suggesting syndromic aortopathy and acquisition of a detailed multigenerational family history are critical. In patients with aortic dissection and syndromic features on physical exam, family history of aortic dissection or other aneurysmal disease and/or experiencing an aortic dissection at less than 60 years old should prompt the clinician to perform genetic testing to evaluate for a pathogenic variant associated with aortic disease.

Long-term management of aortic dissection includes proper blood pressure control with goal blood pressure of 120/80 mm Hg or less. Smoking cessation is essential as active tobacco use is an established risk factor for aortic dissection. Long-term treatment with “anti-impulse” beta-blockade to lower both resting heart rate and systolic blood pressure is recommended. In pregnancy, there are physiologic changes that alter cardiovascular hemodynamics (expanded blood volume, increased cardiac output, elevated heart rate) and hormonal changes that render the aorta more vulnerable to dissection. Thus, women with a history of aortic dissection and/or heritable aortopathy who are contemplating pregnancy should be counseled on the risks of aortic dissection and monitored closely. In regard to lifestyle modifications, strenuous isometric exercises, such as intense weightlifting, can markedly elevate SBP and predispose to dissection; therefore, these activities should be avoided. However, low to moderate aerobic activities and low-stress isometric exercises are generally considered low risk for patients after an aortic dissection.

23 Acute Decompensated Heart Failure

Bria D. Giacomino and Gregory A. Ewald

The clinical syndrome of heart failure (HF) remains an epidemic in the United States. It is estimated that there are 6.7 million Americans living with HF, and 1 million new cases occurring each year. HF is the leading cause of hospitalization for patients aged 65 or over and costs nearly 40 billion dollars per year in the United States. The 1-year mortality from this condition approaches 50% for patients with advanced HF, resulting in greater than 250,000 deaths annually in the United States.

The management of chronic HF has improved substantially during the past two decades. Successful approaches validated by clinical trials have become well established and are documented in numerous evidence-based guidelines. These approaches will not be detailed here but involve (a) modulation of neurohormonal activation, specifically the renin-angiotensin-aldosterone system (via angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], ARB/neprilysin inhibitors [ARNIs], and aldosterone antagonists) and sympathetic nervous system (via beta-blockers); (b) impacting glycemic control and the cardiorenal axis (via sodium-glucose cotransporter 2 inhibitors [SGLT2i]); (c) fluid management (via diuretics and sodium/water restriction); (d) reducing cardiac work and improving cardiac output (via hydralazine, nitrates, and digoxin); and (e) attempting to restore synchronized ventricular contraction and preventing sudden cardiac death (via implantation of biventricular pacemakers and cardiac defibrillators).

In contrast to chronic HF, the management of acute decompensated HF (ADHF) is not as well studied in randomized controlled trials, and evidence-based guidelines have only recently

been developed. There are now three sets of guidelines that provide the clinician with recommendations for treating ADHF, one from the European Society of Cardiology, one from the American College of Cardiology/American Heart Association, and another from the Heart Failure Society of America. Our approach to HF in the critical care setting is consistent with these guidelines and is summarized in this chapter.

ADHF refers to a rapid onset or significant worsening of symptoms and signs of HF. Recognizing these signs is an important first step, as preexisting HF may not have been diagnosed yet or acute HF may present in the setting of myocardial infarction (MI) or acute cardiomyopathy. Patients presenting with ADHF are nearly equally split between those having reduced left ventricular ejection fraction and those with preserved ejection fraction. Typically, patients with ADHF are older, and have a history of hypertension, coronary artery disease, MI, or HF with subjective complaints of paroxysmal nocturnal dyspnea, orthopnea, and dyspnea on exertion. Physical findings that correlate with HF include a third heart sound (S3) and signs of volume overload, including jugular venous distention, hepatojugular reflux, pulmonary rales, and lower extremity edema. Chest radiography may show cardiomegaly or pulmonary venous congestion, but up to 20% of patients with ADHF have none of these findings. Electrocardiographic findings are not specific but may show atrial fibrillation, ventricular hypertrophy, or evidence of prior MI. A completely normal electrocardiogram (ECG) has a high negative predictive value for ADHF.

It is important to remember that although HF is a clinical diagnosis, echocardiography, angiography, and invasive hemodynamic monitoring are useful to document systolic or diastolic dysfunction and monitor the response to therapy. The role of blood testing is limited in the diagnosis of HF; however, B-type natriuretic peptide (BNP) levels can be helpful if the diagnosis is uncertain. Specifically, patients with serum BNP less than 100 pg/mL or NT-proBNP less than 300 pg/mL are very unlikely to have decompensated HF. It is important to note, however, that elevated plasma levels of the natriuretic peptides do not confirm a diagnosis of ADHF because

they can be associated with a variety of other conditions including severely reduced glomerular filtration rate (<60 mL/min), ischemic stroke, liver dysfunction, severe infection, severe burns, and severe metabolic abnormalities. Once the diagnosis of ADHF is confirmed, it is important to determine the precipitating events for the patient's decompensated state and to estimate the patient's mortality risk. Common precipitants of ADHF include myocardial ischemia/infarction, mechanical complications of MI, hypertensive crisis, atrial and ventricular arrhythmias, sepsis, anemia, and decompensation of preexisting HF secondary to medical or dietary nonadherence. Less common precipitating factors include acute myocarditis, peripartum cardiomyopathy, valvular heart disease (including infective endocarditis), pulmonary embolism, cardiac tamponade, drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], negative inotropic agents), and thyrotoxicosis (Table 23.1). Useful laboratory tests to evaluate patients presenting with ADHF are creatinine, blood urea nitrogen, liver function tests (often altered in patients with hypoperfusion or severe congestion), blood counts, and basic electrolytes. Of note, mildly elevated cardiac troponin levels are detected in many patients with ADHF and should not be mistakenly interpreted as evidence of an acute coronary syndrome.

TABLE 23.1 Precipitants of Acute Decompensated Heart Failure

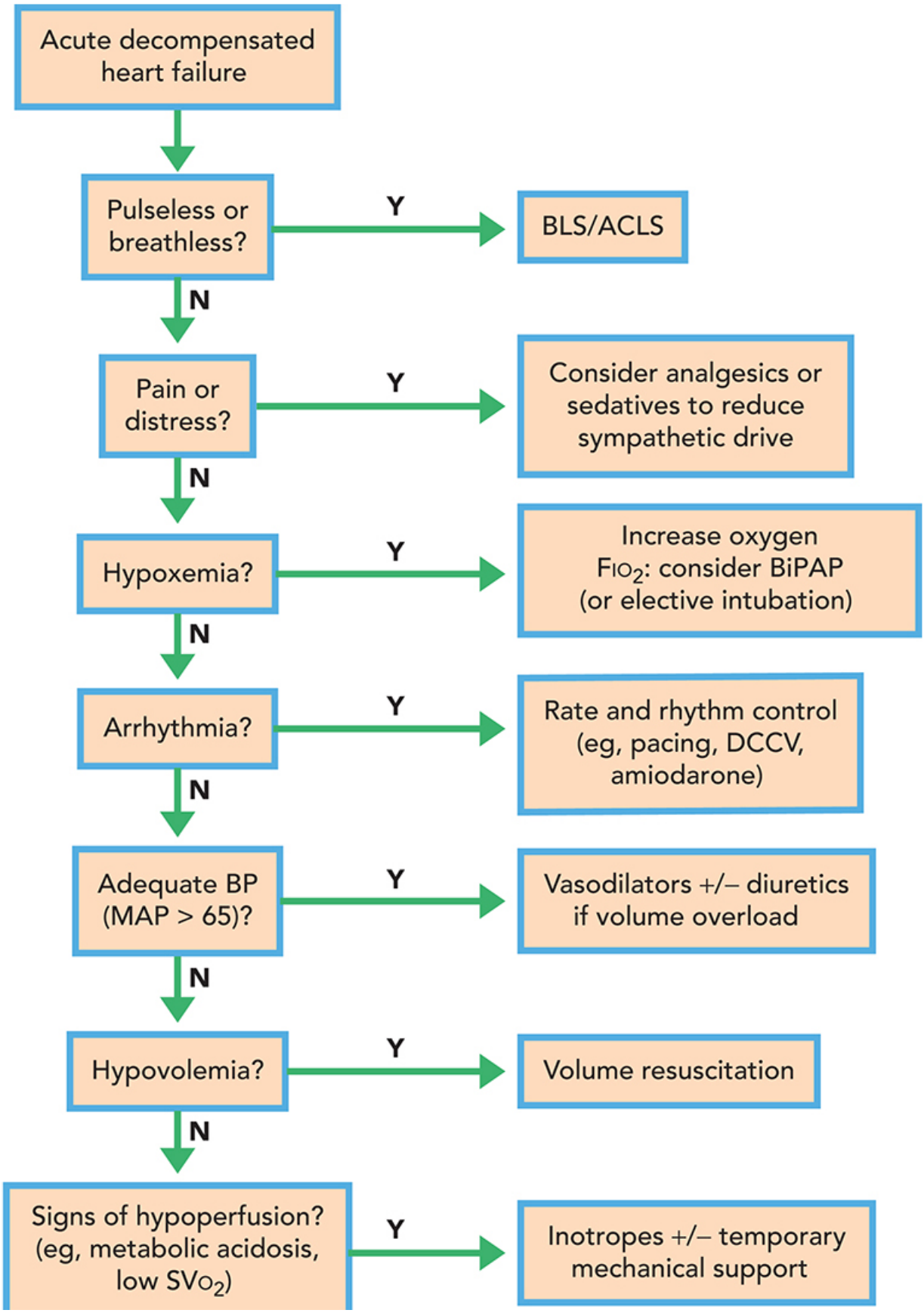
Common	Less Common
Medical/dietary noncompliance	Peripartum cardiomyopathy
Acute myocardial infarction	Acute myocarditis
Hypertensive crisis	Infective endocarditis
Arrhythmias	Valvular heart disease
Sepsis	Cardiac tamponade

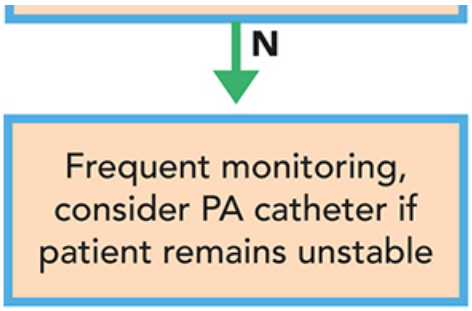
Common	Less Common
Anemia	Thyrotoxicosis

Approximately 4% of patients admitted with ADHF die in the hospital and it is, therefore, critical to identify the patients at highest risk of adverse outcomes. The need for hospital admission is determined primarily by clinical judgment, but admission is always warranted in the presence of dyspnea at rest (typically represented by resting tachypnea or oxygen saturation <90%), hemodynamically significant arrhythmias, worsening renal function, worsening pulmonary congestion, major electrolyte disturbances, or new-onset HF. In most cases, patients with ADHF present with either preserved or elevated blood pressure. Only 5% to 8% of patients present with systolic blood pressure less than 90 mm Hg. These patients have a poor prognosis with an inpatient mortality of more than 16% in the presence of serum creatinine over 2 mg/dL. These patients and those with evidence of hypoperfusion should be considered for admission to an intensive care unit (ICU). An initial algorithmic approach should focus on stabilizing the patient and performing noninvasive assessments of heart rhythm, oxygenation, hemodynamics, and volume status (Algorithm 23.1). This will guide therapies such as amiodarone or cardioversion for atrial fibrillation with rapid ventricular response, vasodilators to reduce afterload and the work of the failing heart, or inotropes for the patient with low cardiac output and inadequate end-organ perfusion. The Forrester classification is useful with either noninvasive data (clinical perfusion status and evidence of pulmonary congestion) or invasive hemodynamic data (Algorithm 23.2). When an accurate clinical assessment of hemodynamic and volume status cannot be made or in the presence of shock, a pulmonary artery catheter (Swan-Ganz) can be useful to measure cardiac index, pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), with the additional benefit of monitoring the response to therapy. However, the placement of a pulmonary artery catheter is not without risks and thus should be reserved for selected cases and only performed by

an experienced operator (see Chapter 85, Pulmonary Artery Catheterization).

ALGORITHM 23.1 Algorithmic Approach to Acute Decompensated Heart Failure

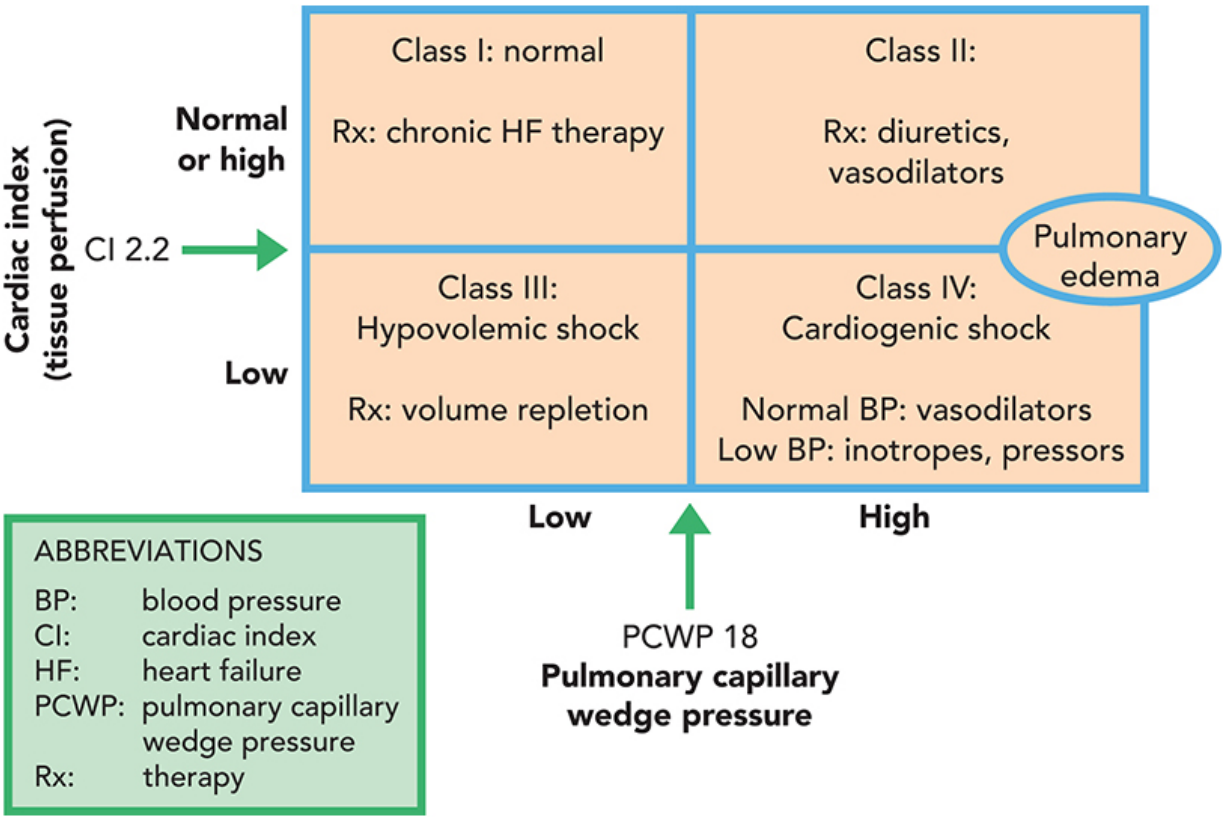

Acute decompensated heart failure
Pulseless or breathless?
Y
BLS/ACLS
N
Pain or distress?
Y
Consider analgesics or sedatives to reduce sympathetic drive
N
Hypoxemia?
Y
Increase oxygen
F_{IO_2}: consider BiPAP (or elective intubation)
N
Arrhythmia?
Y
Rate and rhythm control (eg, pacing, DCCV, amiodarone)
N
Adequate BP (MAP > 65)?
Y
Vasodilators +/– diuretics if volume overload
N
Hypovolemia?
Y
Volume resuscitation
N
Signs of hypoperfusion? (eg, metabolic acidosis, low SVO_2)
Y
Inotropes +/– temporary mechanical support



ABBREVIATIONS

BP:	blood pressure
BLS/ACLS:	basic life support/advanced cardiac life support
BiPAP:	bilevel positive airway pressure
DCCV:	direct current cardioversion
FIO_2:	fraction of inspired oxygen
MAP:	mean arterial pressure
PA:	pulmonary artery
SVO_2:	venous oxygen saturation

ALGORITHM 23.2 Acute Decompensated Heart Failure Therapies by Clinical Presentation (Forrester Classification)



ABBREVIATIONS

BP:	blood pressure
CI:	cardiac index
HF:	heart failure
PCWP:	pulmonary capillary wedge pressure
Rx:	therapy

Treatment

GENERAL MEASURES

Oxygen supplementation should not be routinely used in nonhypoxic patients as oxygen causes vasoconstriction and may decrease cardiac output. Conversely, morphine should be used cautiously; while it can relieve dyspnea and reduce pulmonary vascular resistance (PVR), it can also exacerbate hypotension. If sedation is required for mechanical ventilation support or conscious sedation, cardiodepressive drugs such as propofol can be utilized but should be used with caution. Midazolam is considered to be more hemodynamically neutral and therefore a safer option in patients with ADHF; however, long-term benzodiazepine use carries its own consequences, not limited to increased rates of delirium and prolonged ventilator use. Patients with HF are hypercoagulable; and therefore, deep venous thrombosis (DVT) prophylaxis should be implemented in all patients who are not therapeutically anticoagulated.

MANAGEMENT OF CHRONIC HEART FAILURE MEDICATIONS IN ACUTE DECOMPOSED HEART FAILURE

ACEIs and ARBs have an important role in the management of chronic HF, but their role in the setting of ADHF is less clear. Chronic ACEI or ARB therapy promotes afterload reduction but may require dosage reduction or discontinuation in patients with ADHF to facilitate diuresis without impairment of renal function. Cautious initiation of ACEI or ARB therapy in the ICU setting may be helpful with careful monitoring of renal function and electrolytes. The short-acting ACEI, captopril, at a starting dose of 6.25 to 12.5 mg every 6 to 8 hours may be carefully titrated with each dose until a prespecified goal is met (eg, systolic blood pressure <100 mm Hg, reduced SVR, or 300 mg daily dose). For patients with chronic HF, ACEIs or ARBs should be initiated approximately 48 hours after stabilization of an ADHF episode, most likely after transfer out of the critical care setting (class I recommendation, Level of Evidence A). Fluid restriction (<2 L/d) is recommended in patients with moderate

hyponatremia and is advisable in all patients with fluid overload. In patients with severe hyponatremia, vasopressin receptor antagonists ("vaptans") can be carefully considered. Fluid restriction should be relaxed during treatment with these agents.

Other medical therapies such as beta-blockers and calcium channel blockers have a limited role in the management of patients with ADHF. Beta-blockade is a mainstay of treatment for acute MI as well as for chronic HF, but patients presenting with MI and ADHF involving hypotension or more than mild-to-moderate pulmonary congestion have not been included in most of the relevant clinical trials. As such, intravenous (IV) metoprolol and other beta-blocking agents should be used with caution in this setting. Patients receiving chronic beta-blocker therapy may require a dose reduction, but beta-blockers should not be abruptly discontinued in the absence of hypoperfusion to avoid adverse events related to elevated catecholamine levels. If patients on chronic beta-blockers require inotrope support, milrinone should be considered over dobutamine as it acts downstream from the beta-adrenergic receptor. Nondihydropyridine calcium channel blockers (such as diltiazem and verapamil) are contraindicated in patients with ADHF, secondary to their negative inotropic effects.

DIURESIS

Most patients with ADHF present with volume overload and pulmonary congestion. The mainstays of therapy are diuretics and vasodilators, reserved for those patients with adequate cardiac output to maintain sufficient systolic blood pressure (>85-90 mm Hg) and end-organ perfusion (Algorithm 23.2, Forrester class II) before their initiation. These therapies are considered class I recommendations and reduce the work that must be performed by the failing heart by reducing both preload and afterload while providing symptomatic relief. Initial therapy with IV diuretics (2-2.5 times usual daily oral dose) has a relatively rapid effect, with reductions in right atrial pressure, PCWP, and PVR within 5 to 30 minutes. For patients requiring high doses of furosemide, a

continuous drip may be more practical than bolus dosing. Guidelines for practical diuretic use are shown in Table 23.2 and include adding thiazide diuretics for refractory cases. Patients with significant renal dysfunction and evidence of fluid retention should still be treated with IV diuretics as renal dysfunction often improves with diuresis and decongestion.

TABLE 23.2 Diuretics for Acute Decompensated Heart Failure

Severity of Volume Overload	Diuretic	Dose	Comments
Mild to moderate	Furosemide	20-80 mg PO or IV	Follow Na^+ and K^+
Severe	Furosemide	40-120 mg IV, or IV drip at 2-20 mg/h	Up to every 6 h for bolus dosing
Moderate to severe	Bumetanide	1-4 mg IV, or IV drip at 1-2 mg/h	Follow Na+ and K+ Up to every 6 h for bolus dosing
Refractory to loop diuretics	Add metolazone or chlorothiazide 30 min prior to each furosemide dose.	2.5-5 mg PO 250-500 mg IV	Most helpful when CrCl <30 mL/min
Refractory to combination of loop and thiazide diuretics	Consider inotrope (dobutamine) if renal perfusion is inadequate. Consider renal replacement therapy if renal failure (HD or CVVHDF).		

CrCl, creatinine clearance; CVVHDF, continuous venovenous hemodiafiltration; HD, hemodialysis; IV, intravenous; po, by mouth.

AFTERLOAD REDUCTION

In selected patients with ADHF (such as MI with pulmonary edema), vasodilator therapy with IV nitroglycerin should be considered the first-line agent (Table 23.3). IV nitroglycerin is a balanced arterial and venous vasodilator when given in higher doses, effectively reducing both preload and afterload without impairing tissue perfusion. At low doses, IV nitroglycerin induces venodilation (without significant coronary artery dilation) and may not effectively unload the failing heart. Therefore, IV nitroglycerin should be titrated aggressively (with careful blood pressure monitoring) in patients suffering from ADHF in the setting of myocardial ischemia. In other patients with pulmonary congestion in the setting of ADHF, the combination of IV nitroglycerin and IV loop diuretics provides rapid symptomatic relief and has been found to be more effective than high-dose diuretics alone.

TABLE 23.3 Vasodilators (All Have Potential for Causing Hypotension)

Indication	Vasodilator	Dose	Comments
ADHF	Nitroglycerin	10-200 mcg/min	Headache, tachyphylaxis
ADHF	Nicardipine	0.5-2.5 mcg/kg/min	Reflex tachycardia
Hypertensive crisis	Nitroprusside	0.5-5 mcg/min	Isocyanate toxicity

ADHF, acute decompensated heart failure.

Another potent and more balanced arterial and venous vasodilator is IV nitroprusside. Similar to IV nitroglycerin, IV nitroprusside has a very short half-life and rapid onset of action. However, IV nitroprusside maintains the balanced arterial and venous vasodilation at all doses and may be better tolerated in patients with lower blood pressures on presentation. While nondihydropyridine calcium channel blockers should be avoided in patients with ADHF

due to their myocardial depressive effects, IV nicardipine, a dihydropyridine calcium channel blocker, can be used to reduce afterload in patients with ADHF, as it primarily acts upon vascular smooth muscles. IV nicardipine is predominantly an arterial vasodilator and will have minimal effect on preload; therefore, IV nicardipine may not be the optimal choice for patients with ADHF and volume overload.

ARRHYTHMIAS

Patients with ADHF may additionally present with an arrhythmia, such as atrial fibrillation with rapid ventricular rate or ventricular tachycardia. While increased heart rates can be a compensatory response for acute decompensation to increase cardiac output, higher heart rates can also limit diastolic filling and cardiac output. Therefore, it is important to consider rate and/or rhythm control strategies. Rate control strategies can include IV beta-blockers, IV calcium channel blockers, or digoxin. IV beta-blocker and IV calcium channel blocker use should generally be avoided in patients with ADHF given their myocardial depressive effects. Digoxin should be considered for rate control effects in patients presenting with ADHF, especially in patients with hypotension. Cardioversion (electrical or chemical) should be considered in the setting of hemodynamic compromise but approached with caution in patients who are not consistently anticoagulated before presentation.

INOTROPES AND VASOPRESSORS

For patients in cardiogenic shock with hypotension and evidence of inadequate tissue perfusion (Algorithm 23.2, Forrester group IV), dobutamine and milrinone are the inotropic agents of choice. Dobutamine is predominantly a beta-1- and beta-2-adrenergic receptor agonist, which augments both inotropy and chronotropy. There is frequently a reflex decrease in sympathetic tone that leads to lowered SVR, further augmenting cardiac output. In patients receiving chronic beta-blocker therapy or in patients where

tachycardia is problematic, milrinone is an effective alternative to dobutamine. Milrinone is a type III phosphodiesterase inhibitor with characteristics of both an inotrope and peripheral vasodilator. It has the disadvantage of renal clearance and must be used with caution in patients with acute or chronic renal failure. The peripheral vasodilation of milrinone may also cause hypotension, particularly if it is given inappropriately in the setting of volume depletion (Algorithm 23.2, Forrester class III). Dobutamine and milrinone increase myocardial oxygen demand and should be reserved for cases of documented or suspected cardiogenic shock and systemic hypoperfusion. They do not have a role for mild episodes of ADHF. The use of vasopressors (eg, dopamine or norepinephrine) may also be necessary in urgent situations to maintain blood pressure while the patient is being stabilized, but they should be weaned quickly as they increase afterload and may further reduce end-organ perfusion. Table 23.4 shows typical dosing of inotropic agents and vasopressors.

TABLE 23.4 Inotropic Agents and Vasopressors

Drug	Class	Dose (mcg/kg/min)	Comments
Dobutamine	Inotrope	2.5-10	First line for ADHF
Milrinone	Inotrope/vasodilator	0.25-0.75	Useful with beta-blockade
Dopamine	Inotrope/vasopressor	5-50	Relatively weak agonist
Epinephrine	Inotrope/vasopressor	0.05-0.5	If refractory to dobutamine
Norepinephrine	Vasopressor	0.05-1	More appropriate for sepsis

ADHF, acute decompensated heart failure.

MECHANICAL SUPPORT

For patients who cannot be stabilized with medical therapy, consideration should be given to mechanical circulatory support, particularly if the patient is a candidate for advanced HF therapies such as cardiac transplantation or a durable left ventricular assist device (LVAD). Acute dialysis, especially continuous venovenous hemodialysis, can be used for volume control of selected diuretic refractory patients with renal failure. Intra-aortic balloon pump placement can provide mechanical afterload reduction and augmented diastolic pressure to improve coronary artery filling in low-output states. Several temporary ventricular assist devices (VADs) are now available to provide less invasive short-term mechanical circulatory support. The TandemHeart is a left atrial to femoral artery bypass system capable of providing up to 4 L/min of flow. It consists of an inflow cannula placed into the left atrium from the femoral vein via a transseptal puncture, a continuous flow centrifugal (extracorporeal) pump, and an outflow cannula to the femoral artery. The Impella is an all-arterial percutaneous LVAD that uses a contained microaxial pump placed retrograde across the aortic valve via the femoral or axillary artery. The catheter removes blood from the left ventricular cavity and pumps it into the ascending aorta. Multiple-size Impella devices are available, capable of providing 2.5 to 5.5 L/min of flow. Finally, extracorporeal membrane oxygenation (ECMO) can be used to provide circulatory and respiratory support to bridge patients with severely decompensated HF to definitive therapy with LVAD or heart transplantation. Pursuing more advanced mechanical therapy (eg, LVAD support) or cardiac transplantation is an increasingly viable option for patients without irreversible end-organ damage. Early involvement of advanced HF cardiologists and cardiac surgery specialists is important in such patients to determine candidacy for advanced HF therapies and facilitate institution of appropriate mechanical circulatory support.

SUGGESTED READINGS

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24 Approach to Hypertensive Emergencies

Paul Juang

Hypertensive emergencies have become a less frequent cause for admission to the intensive care unit (ICU) with the widespread availability of antihypertensive medications in the current medical era. Only 1% of patients with hypertension will present with a hypertensive emergency during their lifetime. Unfortunately, severe hypertension is still very common, so distinguishing a true hypertensive emergency from hypertensive urgency is key to guiding therapy. Therefore, the following terms are worth defining.

- Hypertensive crisis: A generic term for severe elevations in blood pressure (BP) that have the potential to cause target organ (heart, vasculature, kidneys, eyes, and brain) damage. This includes both *hypertensive emergency* and *hypertensive urgency.*
- Hypertensive urgency: A severe elevation in BP *without* evidence of acute and ongoing target organ damage (TOD).
- Hypertensive emergency: A severe elevation in BP *with* evidence of acute, ongoing TOD.
  - Hypertensive encephalopathy: A specific hypertensive emergency characterized by irritability, headaches, and mental status changes caused by significant and often, rapid elevations in BP.
  - Accelerated malignant hypertension: A specific hypertensive emergency characterized by fundoscopic findings of papilledema and/or acute retinal hemorrhages and exudates. See Figure 24.1.

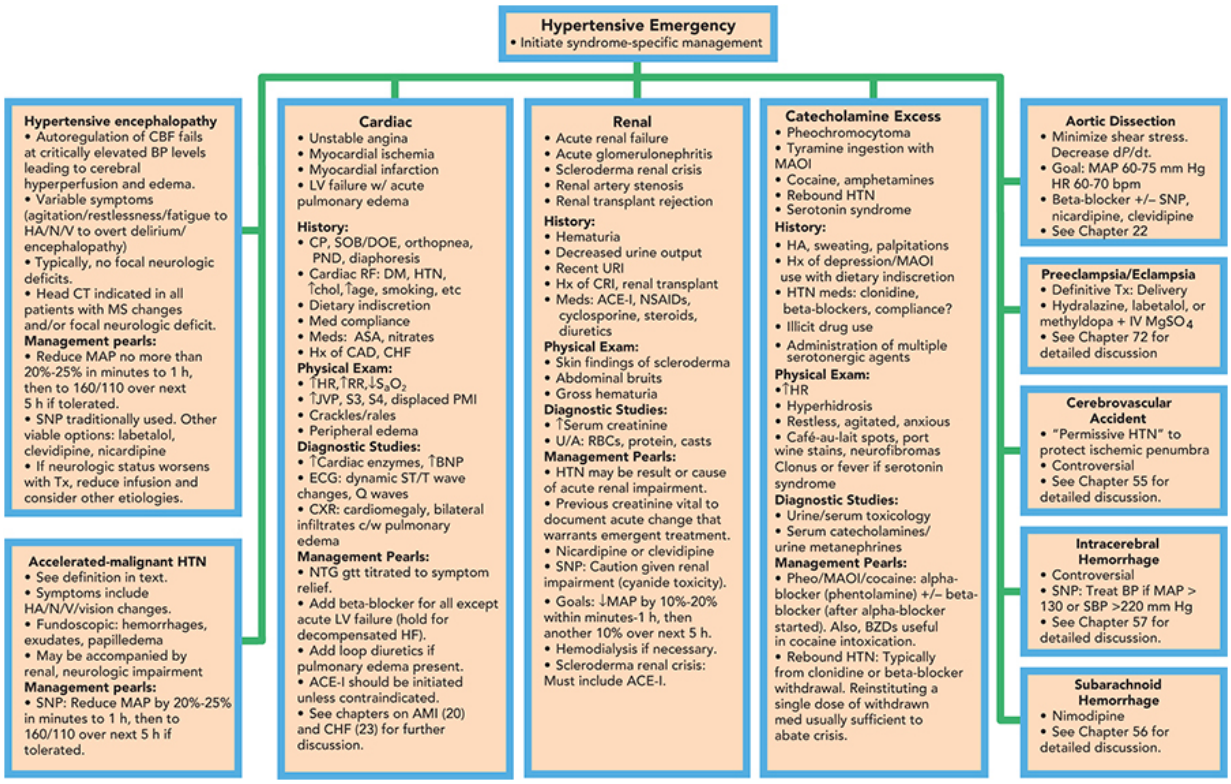

Hypertensive Emergency
• Initiate syndrome-specific management
Hypertensive encephalopathy
• Autoregulation of CBF fails at critically elevated BP levels leading to cerebral hyperperfusion and edema.
• Variable symptoms (agitation/restlessness/fatigue to HA/N/V to overt delirium/encephalopathy)
• Typically, no focal neurologic deficits.
• Head CT indicated in all patients with MS changes and/or focal neurologic deficit.
Management pearls:
• Reduce MAP no more than 20%-25% in minutes to 1 h, then to 160/110 over next 5 h if tolerated.
• SNP traditionally used. Other viable options: labetalol, clevidipine, nicardipine
• If neurologic status worsens with Tx, reduce infusion and consider other etiologies.
Accelerated-malignant HTN
• See definition in text.
• Symptoms include HA/N/V/vision changes.
• Fundoscopic: hemorrhages, exudates, papilledema
• May be accompanied by renal, neurologic impairment
Management pearls:
• SNP: Reduce MAP by 20%-25% in minutes to 1 h, then to 160/110 over next 5 h if tolerated.
Cardiac
• Unstable angina
• Myocardial ischemia
• Myocardial infarction
• LV failure w/ acute pulmonary edema
History:
• CP, SOB/DOE, orthopnea, PND, diaphoresis
• Cardiac RF: DM, HTN, ↑chol, ↑age, smoking, etc
• Dietary indiscretion
• Med compliance
• Meds: ASA, nitrates
• Hx of CAD, CHF
Physical Exam:
• ↑HR,↑RR,↓S_aO_2
• ↑JVP, S3, S4, displaced PMI
• Crackles/rales
• Peripheral edema
Diagnostic Studies:
• ↑Cardiac enzymes, ↑BNP
• ECG: dynamic ST/T wave changes, Q waves
• CXR: cardiomegaly, bilateral infiltrates c/w pulmonary edema
Management Pearls:
• NTG gtt titrated to symptom relief.
• Add beta-blocker for all except acute LV failure (hold for decompensated HF).
• Add loop diuretics if pulmonary edema present.
• ACE-I should be initiated unless contraindicated.
• See chapters on AMI (20) and CHF (23) for further discussion.
Renal
• Acute renal failure
• Acute glomerulonephritis
• Scleroderma renal crisis
• Renal artery stenosis
• Renal transplant rejection
History:
• Hematuria
• Decreased urine output
• Recent URI
• Hx of CRI, renal transplant
• Meds: ACE-I, NSAIDs, cyclosporine, steroids, diuretics
Physical Exam:
• Skin findings of scleroderma
• Abdominal bruits
• Gross hematuria
Diagnostic Studies:
• ↑Serum creatinine
• U/A: RBCs, protein, casts
Management Pearls:
• HTN may be result or cause of acute renal impairment.
• Previous creatinine vital to document acute change that warrants emergent treatment.
• Nicardipine or clevidipine
• SNP: Caution given renal impairment (cyanide toxicity).
• Goals: ↓MAP by 10%-20% within minutes-1 h, then another 10% over next 5 h.
• Hemodialysis if necessary.
• Scleroderma renal crisis: Must include ACE-I.
Catecholamine Excess
• Pheochromocytoma
• Tyramine ingestion with MAOI
• Cocaine, amphetamines
• Rebound HTN
• Serotonin syndrome
History:
• HA, sweating, palpitations
• Hx of depression/MAOI use with dietary indiscretion
• HTN meds: clonidine, beta-blockers, compliance?
• Illicit drug use
• Administration of multiple serotonergic agents
Physical Exam:
•↑HR
• Hyperhidrosis
• Restless, agitated, anxious
• Café-au-lait spots, port wine stains, neurofibromas Clonus or fever if serotonin syndrome
Diagnostic Studies:
• Urine/serum toxicology
• Serum catecholamines/urine metanephrines
Management Pearls:
• Pheo/MAOI/cocaine: alpha-blocker (phentolamine) +/– beta-blocker (after alpha-blocker started). Also, BZDs useful in cocaine intoxication.
• Rebound HTN: Typically from clonidine or beta-blocker withdrawal. Reinstituting a single dose of withdrawn med usually sufficient to abate crisis.
Aortic Dissection
• Minimize shear stress. Decrease d*P*/dt.
• Goal: MAP 60-75 mm Hg HR 60-70 bpm
• Beta-blocker +/– SNP, nicardipine, clevidipine
• See Chapter 22
Preeclampsia/Eclampsia
• Definitive Tx: Delivery
• Hydralazine, labetalol, or methyldopa + IV $MgSO_4$
• See Chapter 72 for detailed discussion
Cerebrovascular Accident
• "Permissive HTN" to protect ischemic penumbra
• Controversial
• See Chapter 55 for detailed discussion.
Intracerebral Hemorrhage
• Controversial
• SNP: Treat BP if MAP > 130 or SBP >220 mm Hg
• See Chapter 57 for detailed discussion.
Subarachnoid Hemorrhage
• Nimodipine
• See Chapter 56 for detailed discussion.

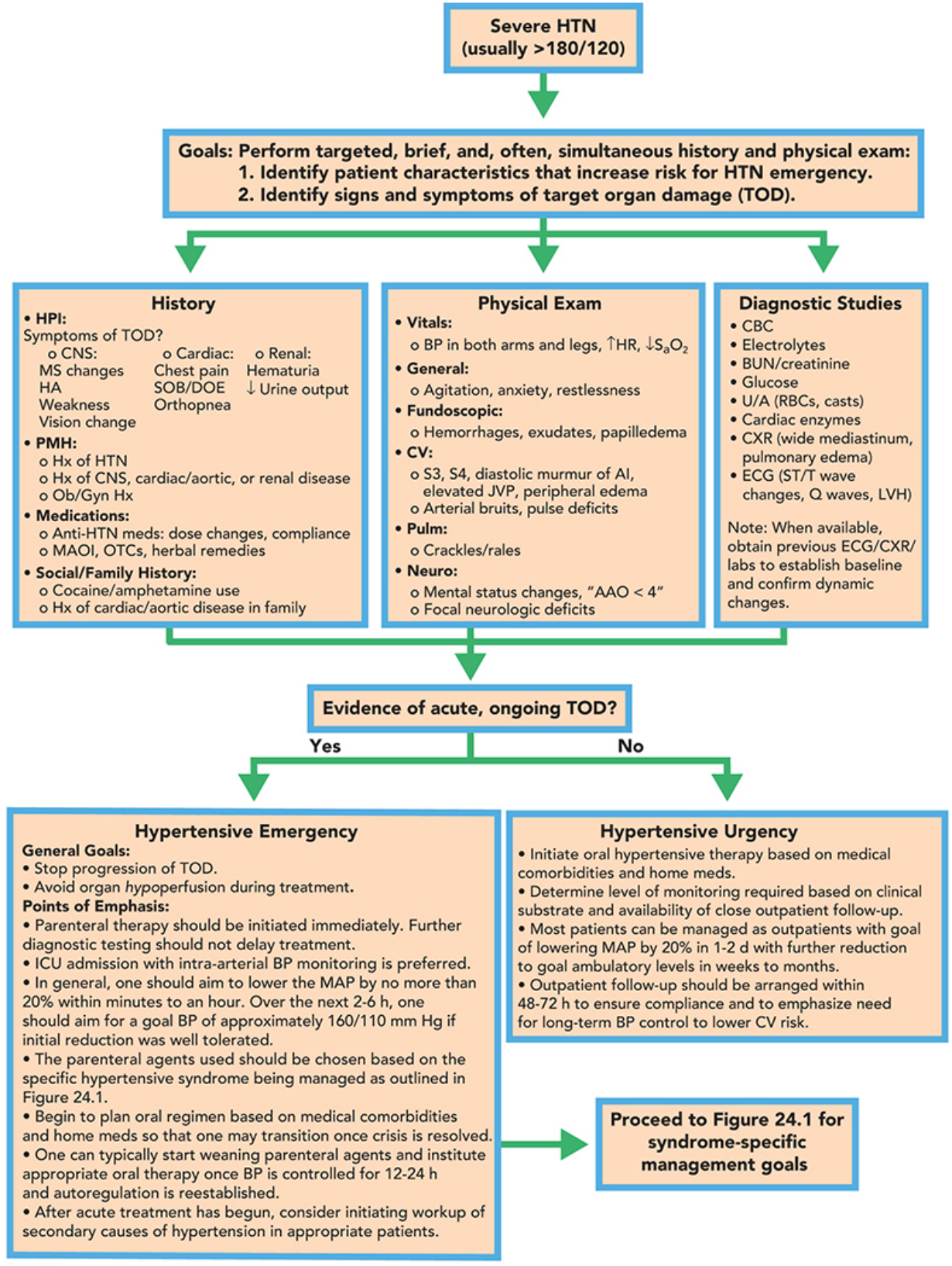
FIGURE 24.1 **Management of specific hypertensive emergencies**. ACE-I, angiotenisin-converting enzyme inhibitor-I; AMI, acute myocardial infarction; BP, blood pressure; CBF, cerebral blood flow; CHF, congestive heart failure; CT, computed tomography; CXR, chest x-ray; DM, diabetes mellitus; d*P*/d*t*, rate of change in pressure; ECG, electrocardiogram; HF, heart failure; HTN, hypertension; LV, left ventricular; MAOI, monoamine oxidase inhibitor; MAP, mean arterial pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; RBCs, red blood cells; SNP, sodium nitroprusside; HA/N/V, headache/nausea/vomiting; MS, mental status; Tx, treatment; CP, chest pain; SOB/DOE, short of breath/dyspnea on exertion; RF, risk factor; Hx, history; PND, paroxysmal nocturnal dyspnea; CAD, coronary heart disease; HR, heart rate; RR, respiratory rate; SaO2, arterial oxygen saturation; JVP, jugular venous pulse; PMI, point of maximal impulse; BNP, brain naturetic peptide; NTG, nitroglycerin; gtt, infusion; URI, upper respiratory tract infection; CRI, chronic renal insufficiency; BZD, benzodiazepine; SBP, systolic blood pressure.

Timely differentiation between hypertensive emergencies and urgencies is imperative so that patients with severely elevated BP can be triaged to the appropriate level of care and monitoring (ie, outpatient follow-up vs inpatient ward vs ICU) with the appropriate antihypertensive agents initiated (parenteral vs oral) and the establishment of BP-lowering goals at the appropriate time interval (minutes to hours vs days to weeks). In the absence of acute, progressive end-organ damage, elevated BP alone does not require immediate, emergent therapy. The definitions mentioned earlier intentionally are devoid of any absolute BP numbers because the level at which individuals develop TOD can vary depending

on clinical substrate and the rapidity with which the BP rises. For example, a patient with long-standing poorly controlled hypertension may tolerate a BP in excess of 230/120 mm Hg without evidence of acute end-organ damage while the young healthy patient who acutely develops glomerulonephritis may become encephalopathic from hypertension at much lower pressures.

The approach to severely elevated BP is outlined in Algorithm 24.1. It should be emphasized that when presented with these patients, one should perform a truncated history and physical exam that (1) quickly identifies patient characteristics that place the patient at risk for hypertensive emergencies and (2) searches for signs and/or symptoms of underlying TOD. If this rapid assessment reveals evidence for a true hypertensive emergency, then treatment should be initiated immediately, preferably in an ICU setting.

ALGORITHM 24.1 **General Approach to Hypertensive Emergencies**


Severe HTN
(usually >180/120)
Goals: Perform targeted, brief, and, often, simultaneous history and physical exam:
1. Identify patient characteristics that increase risk for HTN emergency.
2. Identify signs and symptoms of target organ damage (TOD).
History
• HPI:
Symptoms of TOD?
o CNS: MS changes, HA, Weakness, Vision change
o Cardiac: Chest pain, SOB/DOE, Orthopnea
o Renal: Hematuria, ↓ Urine output
• PMH:
o Hx of HTN
o Hx of CNS, cardiac/aortic, or renal disease
o Ob/Gyn Hx
• Medications:
o Anti-HTN meds: dose changes, compliance
o MAOI, OTCs, herbal remedies
• Social/Family History:
o Cocaine/amphetamine use
o Hx of cardiac/aortic disease in family
Physical Exam
• Vitals:
o BP in both arms and legs, ↑HR, ↓S_aO_2
• General:
o Agitation, anxiety, restlessness
• Fundoscopic:
o Hemorrhages, exudates, papilledema
• CV:
o S3, S4, diastolic murmur of AI, elevated JVP, peripheral edema
o Arterial bruits, pulse deficits
• Pulm:
o Crackles/rales
• Neuro:
o Mental status changes, "AAO < 4"
o Focal neurologic deficits
Diagnostic Studies
• CBC
• Electrolytes
• BUN/creatinine
• Glucose
• U/A (RBCs, casts)
• Cardiac enzymes
• CXR (wide mediastinum, pulmonary edema)
• ECG (ST/T wave changes, Q waves, LVH)
Note: When available, obtain previous ECG/CXR/labs to establish baseline and confirm dynamic changes.
Evidence of acute, ongoing TOD?
Yes
No
Hypertensive Emergency
General Goals:
• Stop progression of TOD.
• Avoid organ hypoperfusion during treatment.
Points of Emphasis:
• Parenteral therapy should be initiated immediately. Further diagnostic testing should not delay treatment.
• ICU admission with intra-arterial BP monitoring is preferred.
• In general, one should aim to lower the MAP by no more than 20% within minutes to an hour. Over the next 2-6 h, one should aim for a goal BP of approximately 160/110 mm Hg if initial reduction was well tolerated.
• The parenteral agents used should be chosen based on the specific hypertensive syndrome being managed as outlined in Figure 24.1.
• Begin to plan oral regimen based on medical comorbidities and home meds so that one may transition once crisis is resolved.
• One can typically start weaning parenteral agents and institute appropriate oral therapy once BP is controlled for 12-24 h and autoregulation is reestablished.
• After acute treatment has begun, consider initiating workup of secondary causes of hypertension in appropriate patients.
Hypertensive Urgency
• Initiate oral hypertensive therapy based on medical comorbidities and home meds.
• Determine level of monitoring required based on clinical substrate and availability of close outpatient follow-up.
• Most patients can be managed as outpatients with goal of lowering MAP by 20% in 1-2 d with further reduction to goal ambulatory levels in weeks to months.
• Outpatient follow-up should be arranged within 48-72 h to ensure compliance and to emphasize need for long-term BP control to lower CV risk.
Proceed to Figure 24.1 for syndrome-specific management goals
ABBREVIATION

BP:	blood pressure	ICU:	intensive care unit
CBC:	complete blood count	JVP:	jugular venous pressure
CNS:	central nervous system	MAP:	mean arterial pressure
CXR:	chest x-ray	MAOI:	monoamine oxidase inhibitor
ECG:	electrocardiogram	LVH:	left ventricular hypertrophy
HPI:	history of present illness	OTC:	over the counter
HR:	heart rate	RBCs:	red blood counts
HTN:	hypertension	SaO2:	arterial oxygen saturation
Hx:	history	TOD:	target organ damage
		U/A:	urinalysis.

The goal of treating hypertensive emergency is to sufficiently lower arterial pressure to stop the progression of TOD without overcorrecting and causing organ hypoperfusion. This careful balance is best achieved with parenteral agents that have a rapid onset and short half-life, administered under the guidance of intra-arterial BP monitoring in an ICU setting. Oral and sublingual agents should not be used as initial treatment for hypertensive emergency due to their variable effects with slower onset and longer half-life. Sodium nitroprusside can be rapidly titrated and is the preferred agent in most hypertensive emergencies. Table 24.1 lists the details of agents used in hypertensive emergencies. One must tailor therapy with syndrome-specific management, as outlined in Figure 24.1.

TABLE 24.1 Parenteral Agents Used in Hypertensive Emergencies

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Sodium nitroprusside	Initial: 0.25-0.50 mcg/kg/min continuous infusion Maint: titrate in increments of 0.5 mcg/kg/min to goal BP up to 8-10 mcg/kg/min continuous infusion	Onset: Seconds Duration: 2-3 min after infusion is stopped	Thiocyanate and cyanide poisoning, nausea, vomiting, ↓BP	• Potent arterial and venous dilator with rapid onset and offset of effect • Use with beta-blocker if used in aortic dissection. • Administer via continuous infusion in ICU, guided by intra-arterial BP monitoring. • Caution in renal or hepatic impairment due to thiocyanate/cyanide accumulation. Signs of toxicity include metabolic acidosis, tremors, seizures, nausea, and vomiting. Thiocyanate levels >10 mg/dL should be avoided. • Avoid prolonged use (>24-48 h) in all patients. Max level infusions should be used for no more than 10 min to limit toxicity. • Increases intracranial pressure but the simultaneous fall in SVR offsets this effect. Therefore, it is still recommended in hypertensive encephalopathy.

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Labetalol	Bolus: 20 mg × 1, then 20-80 mg every 10 min to total dose 300 mg or Bolus then Infusion: 0.5-2 mg/min	Onset: 5-10 min Duration: 3-6 h	↓HR, HB, HF, bronchospasm, nausea, vomiting, flushing	• Combined alpha- and beta-adrenergic blocker • Can be given as IV bolus or IV infusion. Excessive BP drops are unusual. • Useful in most hypertensive emergencies but avoid in CHF and reactive airway disease or COPD as well as 2° or 3° HB or ↓HR. • Commonly used agent (along with hydralazine) in HTN in pregnancy

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Nitroglycerin	Initial: 5 mcg/min Maint: titrate in increments of 0.5 mcg/kg/min every 3-5 min up to 100 mcg/min	Onset: 2-5 min Duration: 5-15 min	Tolerance, HA, ↓BP, nausea, methemoglobinemia	• Similar to SNP, but causes mostly venodilation with only modest arteriolar dilation effects at higher doses. • Most useful in emergencies complicated by cardiac compromise (ie, myocardial ischemia/infarct, LV failure/pulmonary edema). • Also indicated in management of postoperative HTN following CABG. • Avoid use with phosphodiesterase-5 inhibitors and in volume-depleted patients. • Tolerance will develop with prolonged use.

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Hydralazine	Bolus: 10-20 mg every 30 min until goal BP	Onset: 10-30 min Duration: 2-4 h	↓BP, ↑HR, flushing	• Direct arteriolar vasodilator with no significant venous effects. • Caution in patients with CAD or aortic dissection given reflex sympathetic stimulation. Must use with beta-blocker in these patients. • Avoid in patients with increased ICP. • BP-lowering response is less predictable than with above agents and, therefore, use should be limited to HTN in pregnancy if possible.
Enalaprilat	Initial: 1.25 mg × 1, then 1.25-5 mg every 6 h	Onset: 15-30 min Duration: 6-12 h	↓BP, renal failure, hyperkalemia	• The only available IV ACE inhibitor • Response to agent is unpredictable and depends on plasma renin activity and volume status of patient. • Most useful as an adjunctive agent in patients with CHF or scleroderma renal crisis. • Contraindicated in pregnancy and in renal artery stenosis

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Nicardipine	Initial: 5 mg/h, increase by 2.5 mg/h every 20 min up to max dose, 15 mg/h (0.2-1 mcg/kg/min, increase by 0.5 mcg/kg/min up to 1.5 mcg/kg/min)	Onset: 10-30 min Duration: 1-4 h	↓BP, ↑HR, HF, HA nausea, flushing	• Dihydropyridine calcium channel blocker • Can be used effectively in most emergencies, but should be avoided in acute heart failure. • Reflex tachycardia may be avoided with addition of beta-blocker. • Contraindicated in advanced aortic stenosis
Clevidipine	Initial: 1-2 mg/h, double dose every 90 s up to max dose, 32 mg/h	Onset: 2-4 min Duration: 30 min	↓BP, ↑HR, HF, HA nausea	• Dihydropyridine calcium channel blocker • Can be used effectively in most emergencies but should be avoided in acute heart failure. • Reflex tachycardia may be avoided with addition of beta-blocker. • Formulated in 20% lipid emulsion, contraindicated in patients with soybean, soy product, egg and egg product allergy, and in patients with defective lipid metabolism

Drug	Dose	Onset/Duration	Adverse Effects[a]	Points of Emphasis
Esmolol	Bolus: 500 mcg/kg, repeat after 5 min Infusion: 50-100 mcg/kg/min, up to 300 mcg/kg/min	Onset: 1-5 min Duration: 15-30 min	↓HR, HB, HF, bronchospasm, nausea, vomiting, flushing	• Short-acting, cardioselective beta-adrenergic blocker • Useful in ICU patients with variable hemodynamics because of short half-life • Caution in patients with bradycardia and decompensated heart failure
Phentolamine	Bolus: 5-10 mg, repeat q5-15 min Infusion: 0.2-5.0 mg/min	Onset: 1-2 min Duration: 10-20 min	↑HR, HA, nausea	Alpha-adrenergic blocker, used primarily in syndromes associated with excess catecholamines (ie, pheochromocytoma, cocaine/amphetamine toxicity, clonidine withdrawal, MAOI interaction).

↑HR, tachycardia; ↓BP, hypotension; ↓HR, bradycardia; ACE, angiotensin-converting enzyme; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HA, headache; HB, heart block; HF, heart failure; HTN, hypertension; ICP, intracranial pressure; ICU, intensive care unit; IV, intravenous; LV, left ventricle; Maint, maintenance dose; MAOI, monoamine oxidase inhibitor; SNP, sodium nitroprusside; SVR, systemic vascular resistance.

[a]Either common or life-threatening adverse effects of these medications are listed. This does not represent a comprehensive list of all possible adverse effects.

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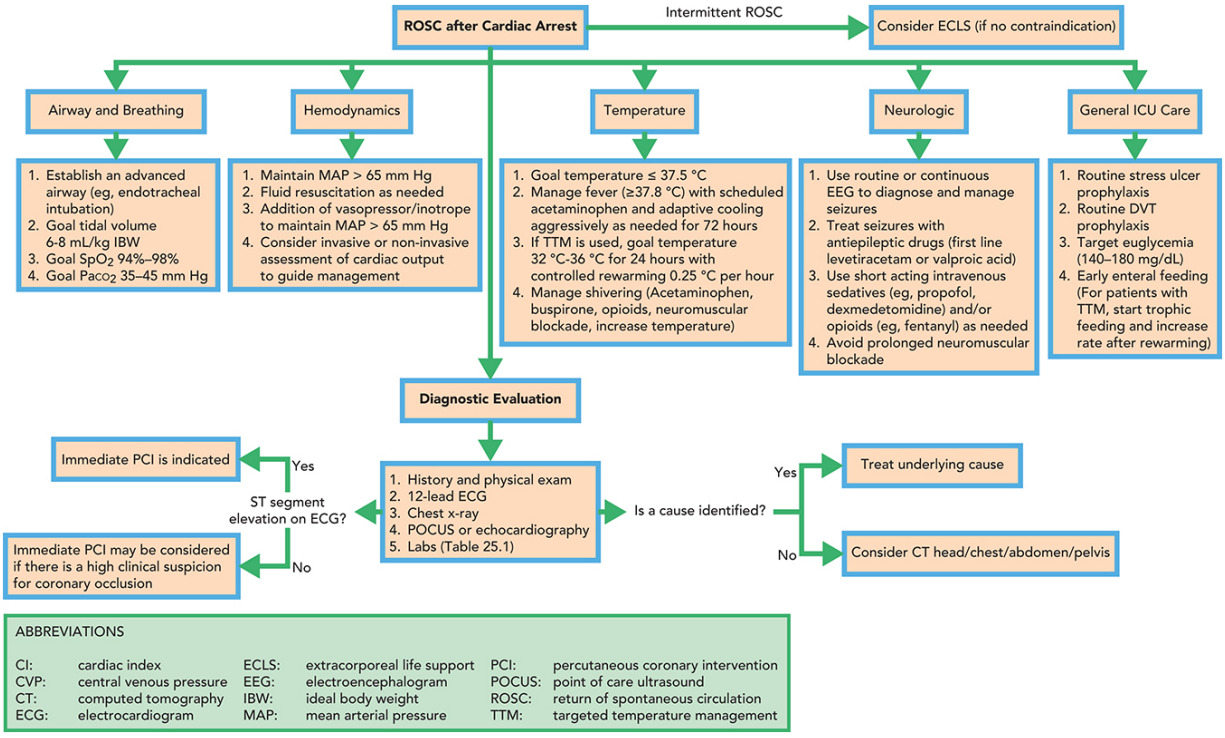
25 Post–Cardiac Arrest Management

John C. Grotberg and Bryan D. Kraft

Sudden cardiac arrest (SCA) affects more than 3.8 million people worldwide annually and survival to hospital discharge remains poor at only 8% to 12%. In the United States alone, there are more than 350,000 out-of-hospital cardiac arrests (OHCAs) and more than 290,000 in-hospital cardiac arrests (IHCAs) annually. Management of the post–cardiac arrest patient is aimed at improving survival as well as neurologic/functional recovery and begins immediately after the return of spontaneous circulation (ROSC). Initial management includes early stabilization of the patient's airway, breathing, and circulation followed by investigation and management of the underlying cause of arrest, including coronary reperfusion if appropriate. Additional key components focus on hemodynamic targets, oxygenation and ventilation targets, temperature management, sedation strategies, neurologic prognostication, and finally rehabilitation and recovery. This chapter will focus on the intensive care unit (ICU) management after SCA (Algorithm 25.1).

ALGORITHM 25.1 Management After Cardiac Arrest


ROSC after Cardiac Arrest
Intermittent ROSC
Consider ECLS (if no contraindication)
Airway and Breathing
Hemodynamics
Temperature
Neurologic
General ICU Care
1. Establish an advanced airway (eg, endotracheal intubation)
2. Goal tidal volume 6-8 mL/kg IBW
3. Goal SpO2 94%–98%
4. Goal Paco2 35–45 mm Hg
1. Maintain MAP > 65 mm Hg
2. Fluid resuscitation as needed
3. Addition of vasopressor/inotrope to maintain MAP > 65 mm Hg
4. Consider invasive or non-invasive assessment of cardiac output to guide management
1. Goal temperature ≤ 37.5 °C
2. Manage fever (≥37.8 °C) with scheduled acetaminophen and adaptive cooling aggressively as needed for 72 hours
3. If TTM is used, goal temperature 32 °C-36 °C for 24 hours with controlled rewarming 0.25 °C per hour
4. Manage shivering (Acetaminophen, buspirone, opioids, neuromuscular blockade, increase temperature)
1. Use routine or continuous EEG to diagnose and manage seizures
2. Treat seizures with antiepileptic drugs (first line levetiracetam or valproic acid)
3. Use short acting intravenous sedatives (eg, propofol, dexmedetomidine) and/or opioids (eg, fentanyl) as needed
4. Avoid prolonged neuromuscular blockade
1. Routine stress ulcer prophylaxis
2. Routine DVT prophylaxis
3. Target euglycemia (140–180 mg/dL)
4. Early enteral feeding (For patients with TTM, start trophic feeding and increase rate after rewarming)
Diagnostic Evaluation
1. History and physical exam
2. 12-lead ECG
3. Chest x-ray
4. POCUS or echocardiography
5. Labs (Table 25.1)
ST segment elevation on ECG?
Yes
Immediate PCI is indicated
No
Immediate PCI may be considered if there is a high clinical suspicion for coronary occlusion
Is a cause identified?
Yes
Treat underlying cause
No
Consider CT head/chest/abdomen/pelvis
ABBREVIATIONS
CI: cardiac index
CVP: central venous pressure
CT: computed tomography
ECG: electrocardiogram
ECLS: extracorporeal life support
EEG: electroencephalogram
IBW: ideal body weight
MAP: mean arterial pressure
PCI: percutaneous coronary intervention
POCUS: point of care ultrasound
ROSC: return of spontaneous circulation
TTM: targeted temperature management

SCA may lead to post–cardiac arrest syndrome, which is defined as a series of complex pathophysiologic processes that include (1) post–cardiac arrest brain injury, (2) post–cardiac arrest myocardial dysfunction, and (3) systemic ischemia/reperfusion response. These processes often occur in the context of the unresolved process that led to the arrest in the first place. Post–cardiac arrest syndrome can be further subdivided into specific intervals of time after ROSC: (1) “immediate” (the first 20 minutes after ROSC), (2) “early” (20 minutes until ~6-12 hours after ROSC), (3) “intermediate” (~6-12 hours until 72 hours after ROSC), and (4) “recovery” (>72 hours after ROSC). These intervals provide a temporal framework through which management, interventions, and prognostication may be viewed.

In the “immediate” post-arrest phase, though a small minority of patients who have a brief period of SCA with immediate return of normal cerebral function and breathing may not require advanced airway management, the vast majority of patients require tracheal intubation if it has not already been performed during cardiopulmonary resuscitation (CPR). Intubation should be performed by skilled personnel. In the absence of skilled personnel,

a supraglottic airway (SGA) can be placed until a provider capable of intubating is available. Blood pressure should be monitored closely for optimal management and prevention of rearrest after ROSC. For patients with intermittent ROSC who otherwise do not have contraindications, extracorporeal life support (ECLS) may be considered (see Chapter 89, ECLS). One should anticipate post-CPR mechanical complications, such as pneumothorax or liver/splenic lacerations in the "immediate" and "early" phases after ROSC.

Investigation of common causes of cardiac arrest (Table 25.1) should also begin immediately and should include evaluations for severe electrolyte or acid/base abnormalities, myocardial injury, hypoglycemia, and infection if indicated (Table 25.2). A 12-lead electrocardiogram (ECG) should be performed to evaluate for signs of myocardial ischemia. Point-of-care ultrasound (POCUS) can assist in the diagnosis of a pericardial effusion, right ventricular dysfunction, left ventricular regional wall motion abnormalities, or intravascular volume depletion that may help determine the cause of arrest. Global biventricular myocardial dysfunction after SCA may also be present and can be determined at the bedside with ultrasonography. For patients without a clear cause of SCA, computed tomography (CT) imaging of the head, chest, abdomen, and pelvis (protocolized as noncontrast head, intravenous contrast with ECG-gated arterial phase of the thorax, and venous phase from the diaphragm to just below the pelvis) should be strongly considered as it has been shown in observational studies to aid in diagnostic evaluation of the etiology of SCA as well as to evaluate for post-resuscitation complications.

TABLE 25.1 Common Mechanisms of Sudden Cardiac Arrest

- **H**ypovolemia (hemorrhage, GI losses, sepsis, anaphylaxis)
- **H**ypoxia (upper airway obstruction, aspiration, asthma/COPD, anaphylaxis)
- **T**amponade (post-cardiotomy, malignancy, trauma, aortic dissection)

- **H**$^{+}$ ions (acidosis) (DKA, acute renal failure, lactic acidosis, shock state)
- **H**ypoglycemia
- **H**ypothermia
- **H**ypokalemia/**H**yperkalemia/**H**ypomagnesemia

- **T**ension pneumothorax
- **T**oxins (overdose, opioids, AV node blocker)
- **T**hrombosis (myocardial infarction, arrhythmia, mechanical complication)
- **T**hromboembolism (pulmonary)
- **T**rauma
- **O**ther (intracranial hemorrhage, cor pulmonale)

AV, atrioventricular; COPD, chronic obstructive pulmonary disease; DKA, diabetic ketoacidosis; GI, gastrointestinal.

TABLE 25.2 Post–Cardiac Arrest Monitoring

Vital Signs/Hemodynamic Monitoring	Laboratory Testing
• Arterial catheter • $ScvO_2$ • Urine output • Pulse oximetry • Waveform capnography • Cardiac output • Continuous temperature	• Glucose • Serum lactate • Arterial blood gas • Electrolytes • CBC • Troponin • Infectious evaluation • Neuron-specific enolase (if available)
Imaging	**Neurologic Monitoring**

Vital Signs/Hemodynamic Monitoring	Laboratory Testing
• Electrocardiogram • Chest x-ray • CT/MRI brain • CT chest/abdomen/pelvis • Echocardiogram	• EEG (continuous or routine) • Neurologic examination • SSEPs

CBC, complete blood count; CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; SSEP, somatosensory evoked potential.

Arrhythmia caused by myocardial ischemia is the most common cause of SCA, and early coronary reperfusion strategies have been investigated in the post-arrest population. If ST segment elevation (STE), or new left bundle branch block (LBBB) is present on ECG following ROSC, emergent percutaneous coronary intervention (PCI) should be pursued as 80% of these patients will have a culprit coronary occlusion. Neurologically favorable survival has been observed in immediate PCI when compared to delayed PCI in patients with STE present on post-ROSC ECG. The absence of STE does not exclude the presence of acute coronary occlusion, and immediate coronary angiography may be considered in patients without STE with a high clinical suspicion of acute coronary occlusion. A large observational study found 30% of patients with OHCA without STE and no apparent noncardiac cause of SCA had a culprit lesion on coronary angiography and successful PCI correlated to favorable outcomes. However, randomized controlled trials have shown no clear benefit to an early versus delayed coronary angiography strategy in patients without STE. Two recent multicenter, randomized controlled trials published in the *New England Journal of Medicine* in 2019 and 2021 evaluated immediate versus delayed (or selective) coronary angiography in OHCA without evidence of STE, enrolling 552 and 530 patients, respectively. There was no difference in survival found between groups. The decision to

pursue immediate or delayed/selective coronary angiography in patients after SCA without STE should be individualized and weigh the clinical suspicion for coronary occlusion, the potential benefits, and potential risks.

Hemodynamics should be optimized to improve cerebral oxygen delivery. However, the optimal hemodynamic targets after SCA remain controversial. Post–cardiac arrest brain injury is a complex physiologic process that in many patients results in the loss of cerebral autoregulation. In this context, cerebral blood flow (CBF) becomes more dependent on the cerebral perfusion pressure (CPP). CPP is the pressure differential between mean arterial pressure (MAP) and intracranial pressure (ICP). Most patients after cardiac arrest will have normal ICP, and therefore, CBF depends directly on MAP (Figure 25.1). While hypotension (sustained MAP <65 mm Hg) is associated with poor outcomes, it is unclear whether patients benefit from high-normal blood pressure targets. An observational study of 51 post-SCA patients using near-infrared spectroscopy (NIRS) to monitor regional cerebral tissue oxygen saturation demonstrated disturbed cerebral autoregulation in 35% of patients. Optimal MAP was determined to be 85 to 90 mm Hg in patients with preserved autoregulation, and 100 to 105 mm Hg in patients with disturbed autoregulation. Time spent with blood pressure below the optimal target was negatively associated with survival (odds ratio [OR] 0.97, 95% CI [0.96:0.99], P = .02). However, randomized trials have failed to demonstrate a clinical benefit targeting a high-normal MAP. For example, a randomized trial evaluating early goal-directed therapy after cardiac arrest randomized patients to a target MAP of 85 mm Hg compared to 65 mm Hg. There were no differences between groups in radiographic evidence of anoxic brain injury or favorable neurologic outcomes. For most patients, targeting a MAP greater than 65 mm Hg is recommended, though a subset of patients, such as those with chronic hypertension, may benefit from a higher blood pressure goal. Volume resuscitation with a balanced crystalloid solution may be warranted, though patients with post-SCA myocardial injury should be closely monitored for signs of elevated intracardiac pressures. Vasopressors and/or inotropes are often

required to achieve target hemodynamics after SCA. In certain populations, mechanical circulatory support (MCS) may be indicated.

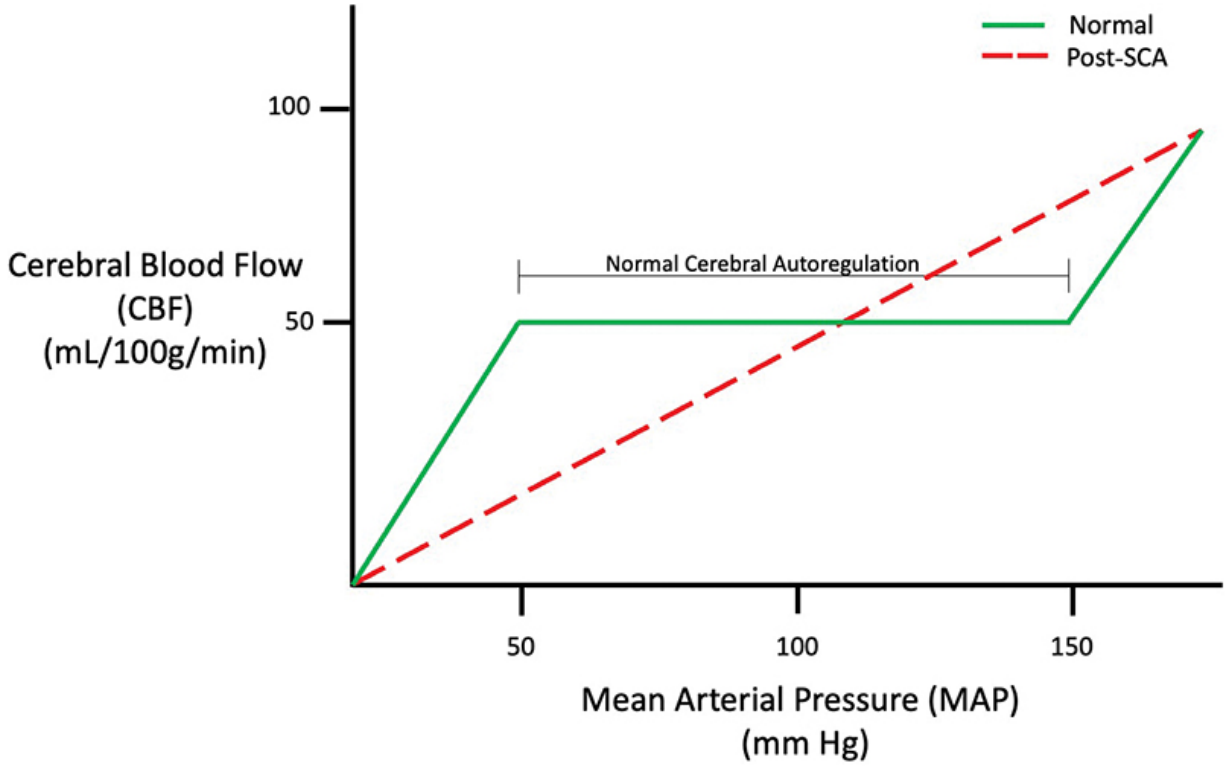


FIGURE 25.1 **Cerebral autoregulation after cardiac arrest.** The relationship between cerebral blood flow (CBF) and mean arterial pressure (MAP) in the setting of constant intracranial pressure. The green line represents normal cerebral autoregulation, while the red dashed line represents dysregulated cerebral autoregulation after cardiac arrest. In healthy patients, the range of MAP with normal autoregulation can vary from patient to patient, and in patients after cardiac arrest, the slope of line directly correlating CBF and MAP can also vary.

As a consequence of post–cardiac arrest syndrome, a subset of patients may develop a systemic inflammatory response syndrome (SIRS), mimicking that of sepsis, and leading to vasodilation and hypotension. However, sepsis can be a cause of SCA, as well as an effect of SCA, for instance, due to aspiration pneumonia. Therefore, patients with signs of SIRS or sepsis should be worked up accordingly. Others, about 50% of post-SCA patients, may develop critical illness-related corticosteroid insufficiency (CIRCI). Thus, there

has been interest over the years of corticosteroid use to mitigate these pathophysiologic processes. However, the use of steroids during or after cardiac arrest remains controversial. Analyses from three trials that studied the administration of corticosteroids during cardiac arrest showed a relative risk of shock reversal of 1.42, of survival to hospital discharge of 1.96, and of good neurologic recovery at hospital discharge of 1.45 in favor of corticosteroids, though CIs did not reach statistical significance. There are limited prospective data, however, to support empiric corticosteroid use in patients post-SCA. The most recent randomized controlled trial published in 2022, the CORTICA trial, randomized 100 patients to receive stress steroids or placebo during and after cardiac arrest. There were no differences between groups related to hemodynamic parameters, body temperature, organ failure–free days, or in-hospital/functional outcomes. At this time there is not sufficient evidence to recommend routine use of low-dose corticosteroids after cardiac arrest.

Oxygenation and ventilation that are critical in patients after cardiac arrest will generally be managed with invasive mechanical ventilation. Oxygenation goals are aimed at avoiding hypoxemia, as this may precipitate (or worsen) ischemic brain injury, and avoiding hyperoxia, as this may worsen brain injury due to oxidant stress. Observational studies have shown an association between hypoxemia and poor outcomes after SCA, and animal models of cardiac arrest have shown worsened neurologic injury when animals are provided 100% oxygen compared with lower oxygen concentrations. Clinicians should target a normal oxygen saturation of 94% to 98%. Patients should undergo lung-protective ventilation with a tidal volume of 6 to 8 mL/kg ideal body weight (IBW). There are mixed data with respect to the optimal arterial partial pressure of carbon dioxide ($PaCO_2$) in patients after cardiac arrest. Extreme hypocapnia and hypercapnia have been associated with poor outcomes. While mild hypercapnia is associated with a lower neuron-specific enolase (NSE), it is unclear if this has any effect in clinical outcomes. Thus, in patients without preexisting chronic

hypercapnia or hypocapnia, a normal range of $PaCO_2$ (35-45 mm Hg) should generally be targeted.

Patients with SCA are at high risk for aspiration, and the administration of prophylactic antibiotics has remained controversial. Though one randomized study found that patients with OHCA treated with prophylactic antibiotics for 48 hours had lower rates of early ventilator-associated pneumonia, a systematic review and meta-analysis including three randomized trials and eight observational studies failed to find any association between survival, neurologic recovery, ICU length-of-stay, or pneumonia in patients who received prophylactic antibiotics. The current evidence suggests against the routine use of prophylactic antibiotics in patients after cardiac arrest.

Temperature management has remained integral to the post-SCA bundle of care. Fever is common in the first 72 hours after cardiac arrest and has been correlated to worse outcomes. Continuous monitoring of core temperature (ie, via bladder or esophageal probe) should be done. Fever should be aggressively managed in the first 72 hours after cardiac arrest with medications and/or with adaptive cooling modalities. Fever also has a differential diagnosis, and febrile patients that are post-SCA should be assessed for infection and other maladies in parallel. Numerous devices are commercially available for cooling and include surface cooling, esophageal cooling, and intravenous cooling. Interest in inducing mild hypothermia in patients after cardiac arrest has stemmed from previous work associated with deep hypothermic circulatory arrest for cardiac surgery. Hypothermia results in a reduction in cerebral oxygen consumption and the cerebral metabolic rate (about 6% for every degree Celsius reduced). Hypothermia may also reduce ischemic-reperfusion injury, neuroinflammation, and free radical production. Hypothermia does not come without risk, however, and may cause bradycardia, blood pressure instability, dysrhythmias, reduced gut motility, coagulopathy, shivering electrolyte derangements, and metabolic derangements. Early targeted temperature management (TTM) with hypothermia became popular

after two landmark papers were published in the *New England Journal of Medicine* in 2002. The HACA trial randomized 275 patients after SCA due to ventricular fibrillation to either hypothermic TTM with a goal of 32 °C to 34 °C or normothermia. Favorable neurologic outcome (cerebral performance category 1 or 2) was observed in 55% of the TTM group compared to 39% of the normothermia group and 6-month mortality was 41% in the TTM group compared to 55% in the normothermia group. Bernard et al randomized 77 patients to receive hypothermia (33 °C within 2 hours after ROSC) or normothermia after SCA. The OR for favorable outcome in the hypothermia group was 5.25 (P = .011). These studies led to further investigation in 2013 with the TTM1 trial comparing 33 °C to 36 °C in patients after OHCA. A total of 939 patients were included in the primary analysis of all-cause mortality. There were no significant differences in all-cause mortality or neurologically favorable outcomes between groups. The HYPERION trial in 2019 compared 33 °C to normothermia in patients with OHCA and an initial non-shockable rhythm. A total of 581 patients were included in the primary analysis and there was increased 90-day neurologically favorable survival (10.2% compared to 5.7%, P = .04) in the hypothermia group. This led to the most recent and largest trial to date, the TTM2 trial, published in 2021. The TTM2 trial randomized 1,900 patients with OHCA to hypothermia (33 °C) or normothermia (≤37.5 °C) with early treatment of fever (≥37.8 °C); 1,850 patients were included in the final analysis. There were no significant differences between groups in 6-month mortality or neurologically favorable outcomes. Higher rates of arrhythmia resulting in hemodynamic compromise were observed in the hypothermia group. With the addition of the TTM2 trial, the evidence suggests that aggressive management and prevention of fever is likely equivalent to induced hypothermia after cardiac arrest, no matter the initial rhythm, without subjecting patients to the potential harms of hypothermia. However, this still remains a controversial topic in the management of comatose patients after SCA as there still may be a subset of patients who benefit from early therapeutic hypothermia. Certainly the evidence suggests all patients should

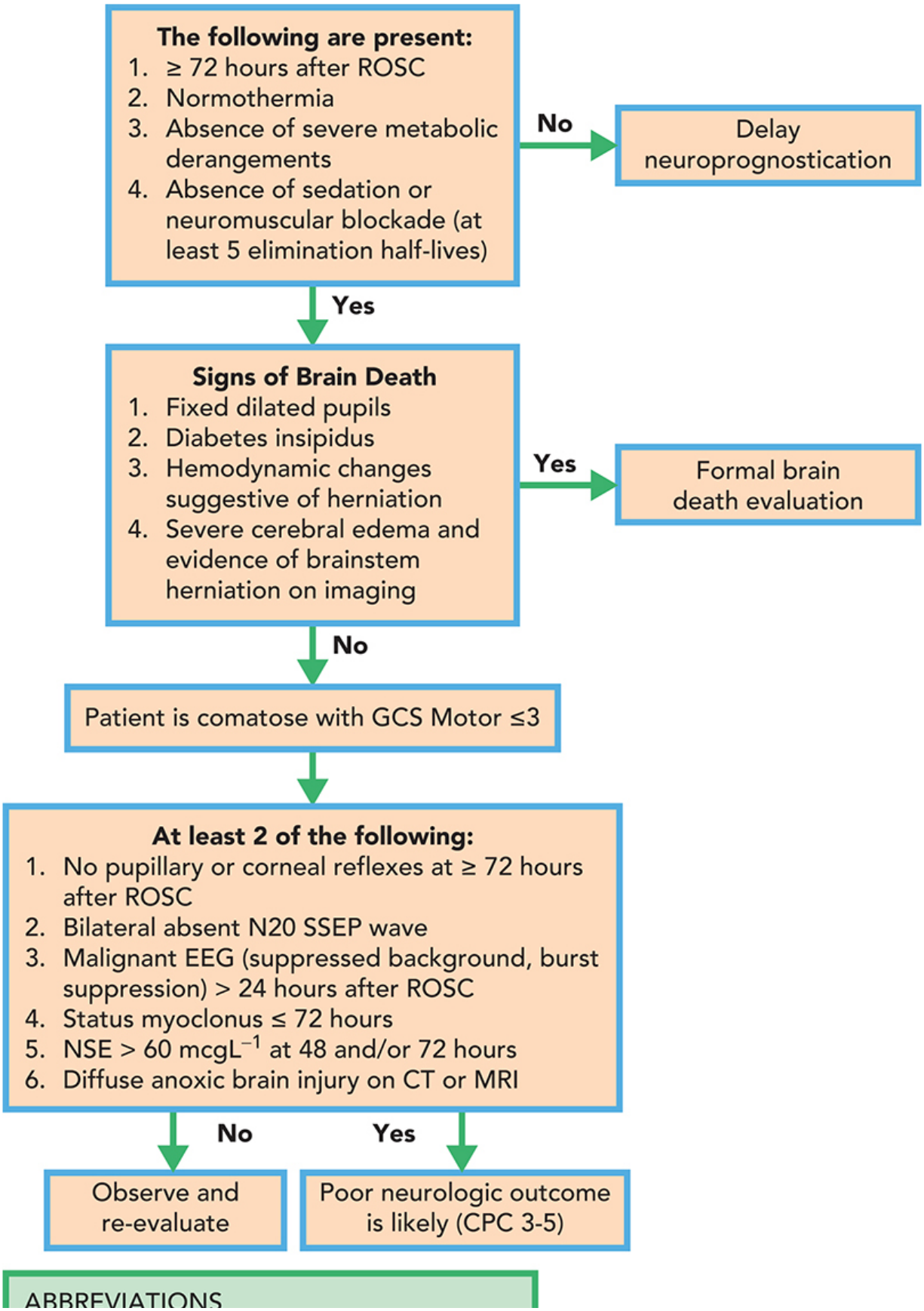
undergo aggressive management and prevention of fever for the first 72 hours after ROSC. Patients that are selected to undergo therapeutic TTM should target a temperature of 32 °C to 36 °C for at least 24 to 48 hours followed by controlled rewarming of 0.25 °C per hour. Shivering may be managed pharmacologically (eg, opioids, sedatives). Long durations of neuromuscular blockade should be avoided as they interfere with the neurologic exam, though it may be used as a last resort to control shivering.

Patients with severe ischemic brain injury after cardiac arrest are at high risk for the development of seizures and studies suggest this occurs in about 20% to 30% of comatose patients after SCA. Seizures may be recognized clinically as convulsions, or electrographically (non-convulsive) using electroencephalography (EEG). Continuous EEG may be helpful at identifying non-convulsive status epilepticus in comatose patients after SCA, though there is no demonstrated benefit between continuous and routine EEG in this patient population. Antiepileptic drugs (AEDs) should be used to manage seizures (ie, levetiracetam, valproic acid, fosphenytoin, lacosamide). There is no evidence to suggest the prophylactic use of AEDs. The presence of shivering can mimic or confound the presence of seizures, either clinically or electrographically, and the administration of a short-acting paralytic may aid in differentiating between the two.

Roughly two-thirds of in-hospital deaths in comatose patients after OHCA result from hypoxic-ischemic brain injury. The majority of these occur in the setting of withdrawal of life-sustaining treatment (WLST) where the severity of brain injury is indicative of a poor neurologic outcome. Therefore, neurologic prognostication after cardiac arrest is crucial to avoid inappropriate withdrawal of care. The timing of prognostication is critical as well. For example, brain death cannot be declared until at least 24 hours after ROSC or rewarming to normothermia (see Chapter 59, Declaration of Brain Death). In the absence of brain death, neurologic prognostication cannot be assessed until at least 72 hours after ROSC (Algorithm 25.2) and should occur in the absence of hypothermia, severe metabolic derangements, sedation, or neuromuscular

blockade. In general, short-acting sedatives, such as propofol or dexmedetomidine, should be used if sedation is indicated. Neuromuscular blockade should be avoided unless absolutely necessary. In this context, the clinical examination should be delayed until at least five elimination half-lives of the drug administered with the longest half-life have passed, but may require even more time in the setting of acute or chronic renal or hepatic dysfunction, which may alter pharmacokinetics, particularly in drugs with active metabolites. Prognostication consists of multimodal testing involving physical examination, serum biomarkers (when available), and functional neurologic testing and imaging. Outcomes of neurologic/functional status are often measured by the Cerebral Performance Categories (CPC) or modified Rankin Score (mRS). Recent large systematic reviews and meta-analyses have been conducted involving both patients who underwent induced hypothermia, and those that did not, including more than 87 studies. Predictors of poor neurologic outcome (CPC 3-5) included the presence of status myoclonus at 24 to 48 hours, bilateral absence of somatosensory evoked potential (SSEP) N20 wave, malignant EEG activity (suppressed background or burst suppression) at 24 to 72 hours, absence of pupillary and corneal reflexes at 72 hours, NSE > 60 $mcgL^{-1}$ at 48 and/or 72 hours, and diffuse anoxic brain injury on CT or magnetic resonance imaging (MRI). In comatose patients after SCA with a Glasgow Coma Scale motor response less than or equal to 3 (M ≤ 3) at 72 hours or more after ROSC in the absence of confounders, poor neurologic outcome is likely (0% false positivity rate) when at least two of the aforementioned predictors are present (Algorithm 25.2). Patients diagnosed with brain death, or those predicted to have poor neurological recovery for whom family is pursuing WLST, should be considered for organ donation if appropriate.

ALGORITHM 25.2 **Neuroprognostication After Cardiac Arrest**


The following are present:
1. ≥ 72 hours after ROSC
2. Normothermia
3. Absence of severe metabolic derangements
4. Absence of sedation or neuromuscular blockade (at least 5 elimination half-lives)
No
Delay neuroprognostication
Yes
Signs of Brain Death
1. Fixed dilated pupils
2. Diabetes insipidus
3. Hemodynamic changes suggestive of herniation
4. Severe cerebral edema and evidence of brainstem herniation on imaging
Yes
Formal brain death evaluation
No
Patient is comatose with GCS Motor ≤3
At least 2 of the following:
1. No pupillary or corneal reflexes at ≥ 72 hours after ROSC
2. Bilateral absent N20 SSEP wave
3. Malignant EEG (suppressed background, burst suppression) > 24 hours after ROSC
4. Status myoclonus ≤ 72 hours
5. NSE > 60 mcgL^{-1} at 48 and/or 72 hours
6. Diffuse anoxic brain injury on CT or MRI
No
Yes
Observe and re-evaluate
Poor neurologic outcome is likely (CPC 3-5)
ABBREVIATIONS

CPC:	cerebral performance categories
CT:	computed tomography
EEG:	electroencephalogram
GCS:	glasgow coma scale
MRI:	magnetic resonance imaging
NSE:	neuron specific enolase
ROSC:	return of spontaneous circulation
SSEP:	somatosensory evoked potential

In conclusion, SCA is a highly prevalent event that has numerous causes and carries a high risk for morbidity and mortality. The ICU management is primarily focused on the airway, oxygenation, ventilation, hemodynamics, temperature, and neurologic sequelae of severe ischemic brain injury while simultaneously evaluating and treating the initial cause of cardiac arrest. Prognostication is a key component of ICU care after SCA, and should occur at least 72 hours after ROSC. As resuscitation science advances and large clinical trials continue to evaluate the results of current practices and interventions, we will likely continue to see the landscape shift in post–cardiac arrest management.

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SECTION IV Electrolyte Abnormalities

26 Electrolyte Abnormalities

Taha Mohamed Djirdeh and Seth Goldberg

Disorders of Water Balance

Hyponatremia and hypernatremia are primarily disorders of *water* balance (osmoregulation) or *water* distribution across the various fluid compartments in the body. The countercurrent mechanisms of the kidneys in concert with the hypothalamic osmoreceptors via antidiuretic hormone (ADH) secretion and aquaporin insertion maintain a very finely tuned balance of water. When the serum osmolality becomes too dilute (<280 mOsm/kg), excess water is excreted by the kidneys as dilute urine. Conversely, when the serum osmolality becomes too concentrated (>290 mOsm/kg), the release of ADH and development of thirst result in water retention in order to bring the system back into balance. Defects in such handling of water present as hyponatremia or hypernatremia (Figure 26.1).

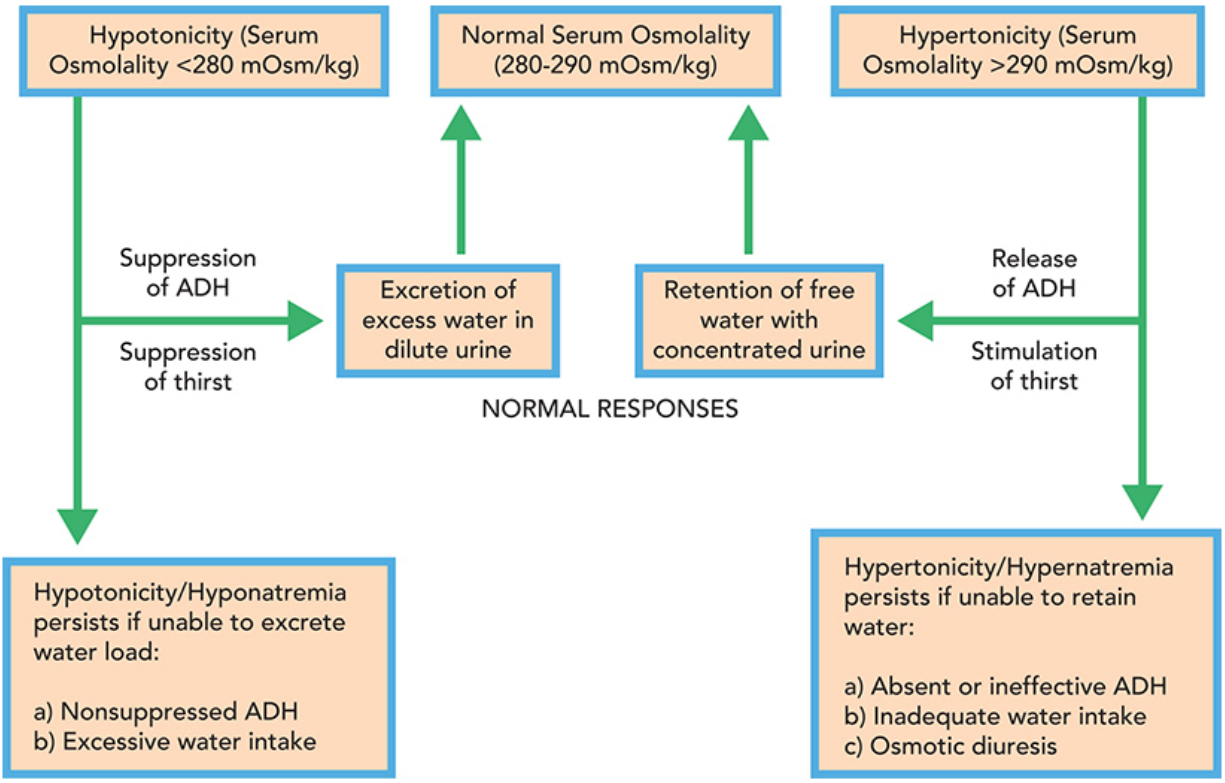


FIGURE 26.1 **Regulation of osmolality**. ADH, antidiuretic hormone.

An important concept in distinguishing water (osmotic) balance from volume homeostasis is to understand the difference between Na^+ *concentration* and the *total body* Na^+ balance. Osmotic disorders are represented by abnormalities in the serum sodium concentration (hyponatremia or hypernatremia), while volume disorders resulting from too much or too little total body sodium manifest as changes in the physical examination. These are regulated independently, where osmoregulation is mediated by ADH and thirst, while volume regulation is driven by the renin-angiotensin-aldosterone system, atrial natriuretic peptide, and the sympathetic nervous system (Figure 26.2). ADH can perform a small overlapping role in volume regulation, where it can maintain volume, but this would be at the expense of osmolality.

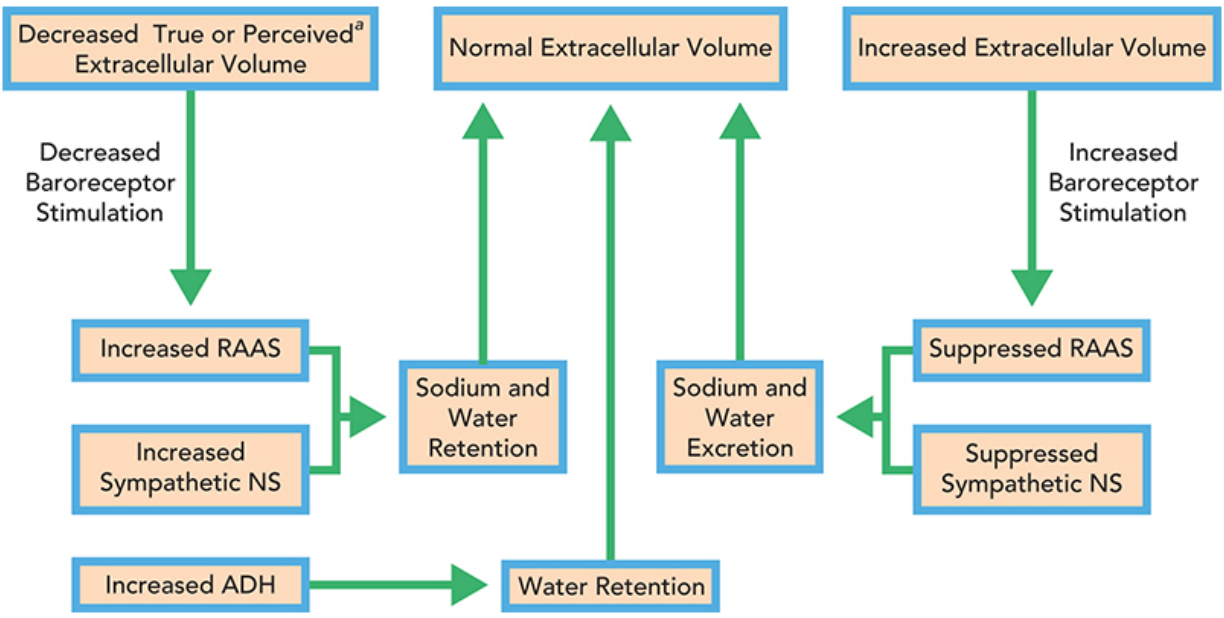


FIGURE 26.2 **Regulation of extracellular volume**. ADH, antidiuretic hormone; NS, nervous system; RAAS, renin-angiotensin-aldosterone system. [a]Decreased perceived extracellular volume occurs in decompensated congestive heart failure and cirrhosis, leading to a maladaptive sodium-avid state and edema.

The incidence of hyponatremia and hypernatremia in the intensive care unit (ICU) is each reported to be approximately 15% to 30%. The significance of both lies not only in their direct clinical effects in the individual patient but also as prognostic factors regarding mortality. The in-hospital mortality of patients with either hyponatremia or hypernatremia is approximately 30% to 40%, which is significantly greater relative to eunatremic patients.

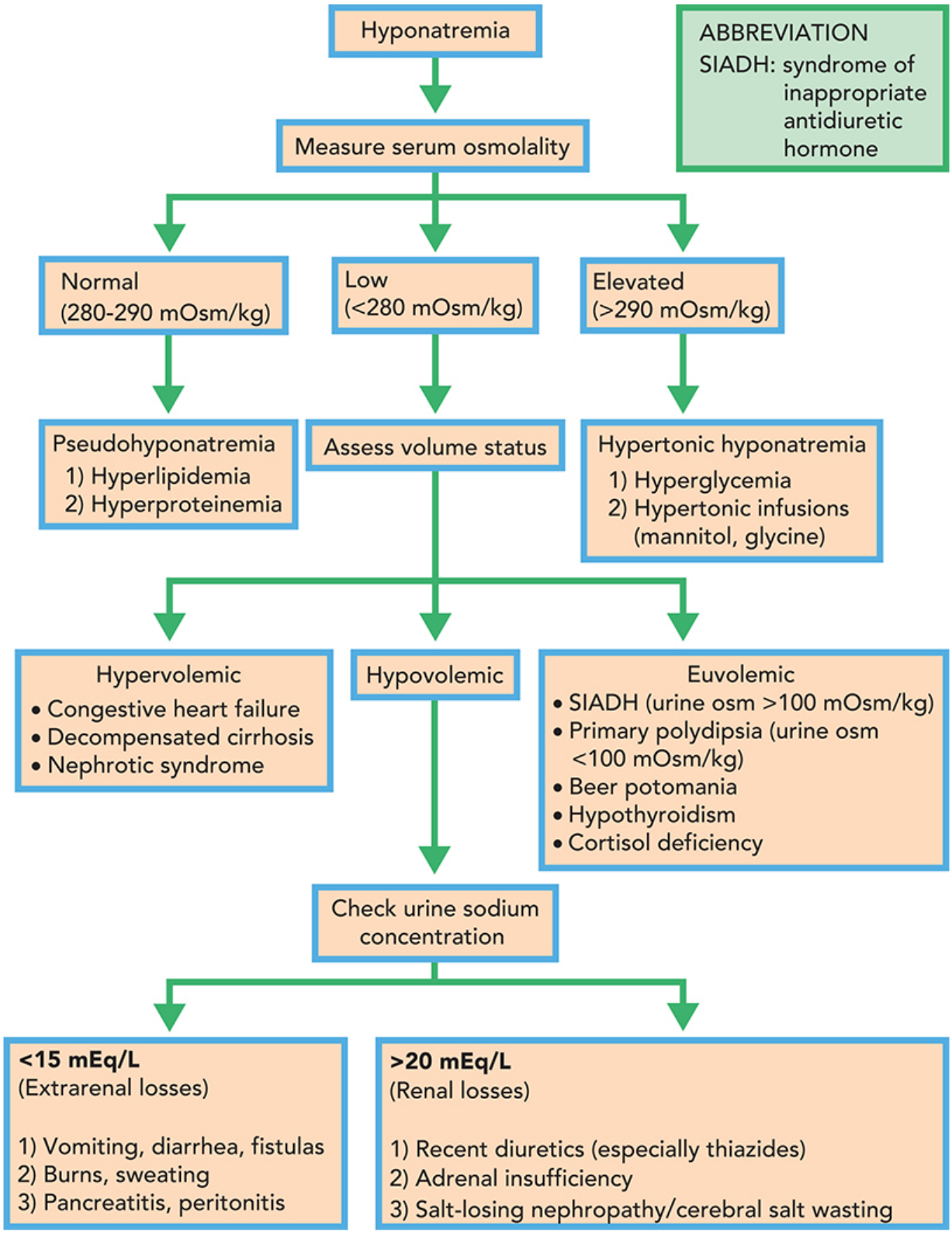
The organ most sensitive to osmotic shifts is the brain. As such, the symptoms of hyponatremia and hypernatremia predominantly involve the nervous system as water shifts into or out of neuronal cells. Hypotonicity results in water entry, leading to cell swelling within the fixed cranial vault (with risk of herniation), while hypernatremia results in cell shrinkage and the risk of tearing the brain away from the meninges (with potential hemorrhage). The severity of clinical symptoms often depends on the *acuity* of the disturbance and not just the *magnitude*, as neurons have the capability to adapt to gradual changes over 48 hours. Hyponatremia and hypernatremia can present

with similar symptomatology, ranging from headache to confusion, stupor, seizures, and coma.

HYPONATREMIA

When evaluating a patient for hyponatremia (Algorithm 26.1), one should first confirm that the low [Na^+] reflects a genuinely hypotonic state by checking the serum osmolality. If the serum osmolality is within the normal range, “pseudohyponatremia,” a measurement artifact, is likely present. However, if there is an elevated serum osmolality, a hypertonic disorder (eg, hyperglycemia, mannitol) is responsible for water shifting out of cells, diluting the serum [Na^+]. If there is indeed hypotonic hyponatremia, the patient’s volume status can help determine if the cause of hypotonicity is from “appropriate” ADH secretion in response to a volume stimulus, such as from true hypovolemia or from a perceived decrease in effective circulating volume leading to an edematous state (eg, heart failure, liver failure). If the patient is euvolemic, the cause is either from “inappropriate” ADH secretion (ie, not mediated by an osmotic or volume stimulus) or from hypotonic fluid loading such as primary polydipsia; these can be distinguished from each other by urine osmolality, which should be maximally dilute (<50-100 mOsm/kg) if ADH is appropriately suppressed.

ALGORITHM 26.1 **Evaluation of Hyponatremia**


Hyponatremia
ABBREVIATION
SIADH: syndrome of inappropriate antidiuretic hormone
Measure serum osmolality
Normal (280-290 mOsm/kg)
Low (<280 mOsm/kg)
Elevated (>290 mOsm/kg)
Pseudohyponatremia
1) Hyperlipidemia
2) Hyperproteinemia
Assess volume status
Hypertonic hyponatremia
1) Hyperglycemia
2) Hypertonic infusions (mannitol, glycine)
Hypervolemic
• Congestive heart failure
• Decompensated cirrhosis
• Nephrotic syndrome
Hypovolemic
Euvolemic
• SIADH (urine osm >100 mOsm/kg)
• Primary polydipsia (urine osm <100 mOsm/kg)
• Beer potomania
• Hypothyroidism
• Cortisol deficiency
Check urine sodium concentration
<15 mEq/L
(Extrarenal losses)
1) Vomiting, diarrhea, fistulas
2) Burns, sweating
3) Pancreatitis, peritonitis
>20 mEq/L
(Renal losses)
1) Recent diuretics (especially thiazides)
2) Adrenal insufficiency
3) Salt-losing nephropathy/cerebral salt wasting

ETIOLOGIES OF SPECIAL IMPORTANCE IN THE CRITICALLY ILL PATIENT

Hyperglycemia (Hypertonic Hyponatremia)

Glucose acts as an osmotically active solute because it is restricted to the extracellular fluid (ECF) in states of insulin deficiency. In the marked hyperglycemia of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states, the ECF hyperosmolality (usually >290 mOsm/kg) causes water to shift from the intracellular fluid (ICF) compartment to the ECF, resulting in dilutional hyponatremia. The plasma [Na^+] falls by approximately 2 mEq/L for every 100 mg/dL rise in the plasma glucose above normal.

Edematous States (Hypervolemic Hypotonic Hyponatremia)

Heart failure and cirrhosis result in a decreased “effective circulating volume.” Given the primacy of volume preservation, the body’s response to this perceived threat is to hold onto salt and water, with ADH release as part of the response. Thus, water excretion is submaximal. The degree of hyponatremia correlates with the severity of the underlying condition, having been shown to be a poor prognostic indicator in heart failure patients.

Syndrome of Inappropriate Antidiuretic Hormone (Euvolemic Hypotonic Hyponatremia)

ADH has overlapping roles in osmotic and volume balance. “Inappropriate” ADH secretion refers to release of ADH that is responding to neither of these stimuli. Patients with the syndrome of inappropriate antidiuretic hormone (SIADH) are euvolemic, indicating that a true or perceived volume deficit is not the stimulus for ADH production. The urine osmolality is inappropriately concentrated (>100 mOsm/kg) for the prevailing hypotonic state, indicating the presence of ADH. Commonly associated conditions include neuropsychiatric disorders (eg, meningitis, encephalitis, acute psychosis, cerebrovascular accident, head trauma), pulmonary diseases (eg, pneumonia, tuberculosis, positive pressure ventilation, acute respiratory failure), malignant tumors (most commonly small cell lung

cancer), and physical/emotional stress and pain. Before making the diagnosis of SIADH, pharmacologic agents that enhance ADH action must be withdrawn.

- Nicotine, carbamazepine, antidepressants, narcotics, antipsychotic agents, and certain antineoplastic drugs may stimulate ADH release.
- Chlorpropamide, methylxanthines, and nonsteroidal anti-inflammatory drugs (NSAIDs) potentiate the action of ADH.
- Oxytocin and desmopressin acetate are ADH analogs.

Also, deficiencies of thyroid hormone or cortisol can present with euvolemic hyponatremia and should be ruled out.

It is often difficult to differentiate SIADH from true hypovolemia since both clinical scenarios are driven by ADH and both will have low serum osmolality and high urine osmolality. Measuring the urine sodium (typically <20 mEq/L with volume depletion, >40 mEq/L with untreated SIADH) and serum uric acid (normal or elevated with volume depletion, low with SIADH) may help in making this differentiation.

Cerebral Salt Wasting (Hypovolemic Hypotonic Hyponatremia)

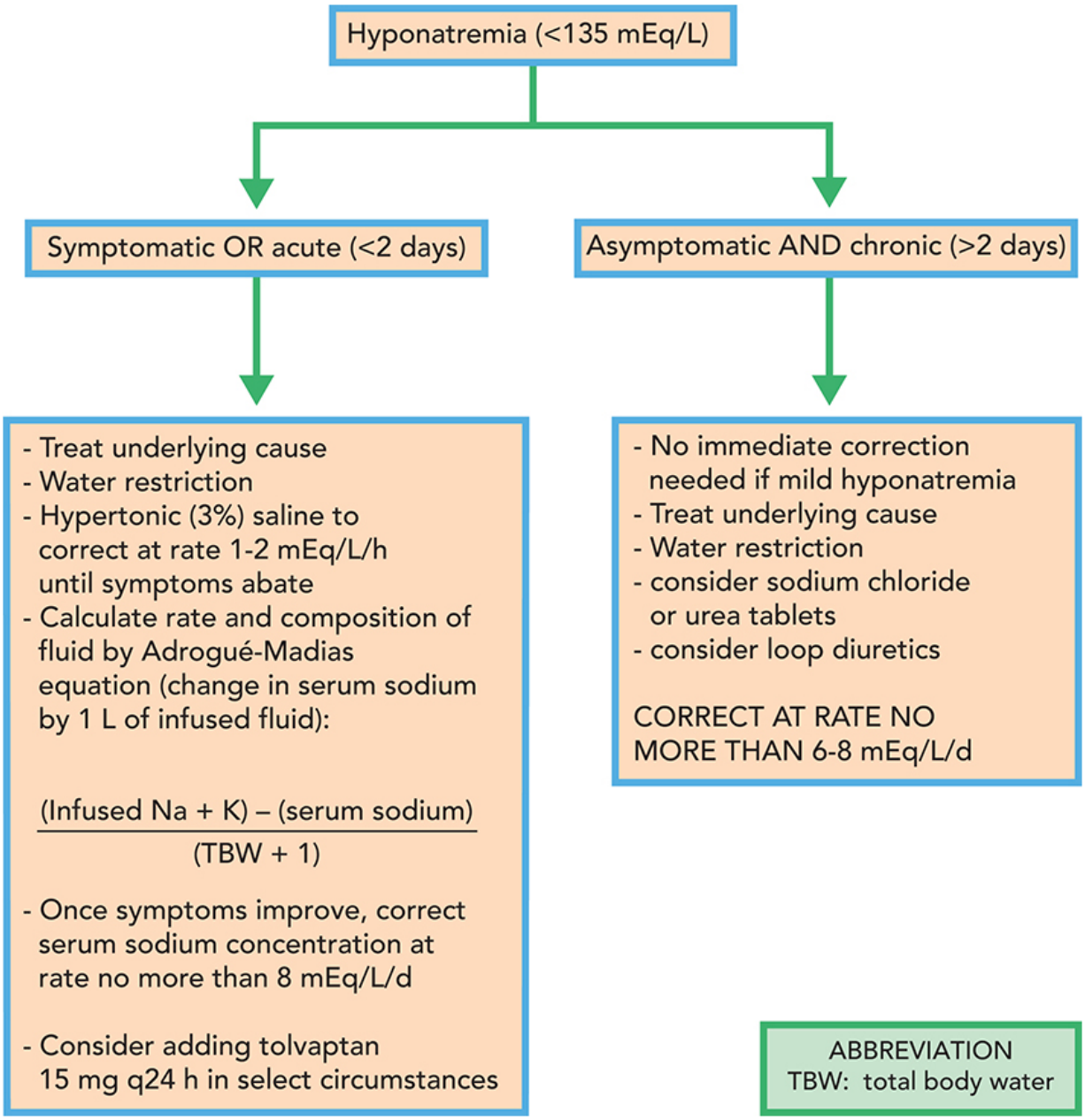
Neurosurgery and central nervous system trauma, especially subarachnoid hemorrhage, may be associated with excessive renal Na^+ excretion. Although not well understood, the mechanism may involve the release of a brain natriuretic peptide and/or the loss of renal sympathetic tone. The loss of Na^+ results in volume depletion, which leads to the release of ADH. This volume depletion is the main feature that distinguishes cerebral salt wasting from SIADH. The hyponatremia, however, does not always correct with volume resuscitation, perhaps as a result of concomitant ADH release from the damaged brain. In some cases, the use of fludrocortisone can ameliorate the decline in [Na^+].

TREATMENT

The hyponatremia in an *isotonic* state is usually of little clinical significance as fluid shifts and neuronal swelling do not occur. With *hypertonic* hyponatremia, cellular dehydration may occur, and correction centers on metabolizing or removing the osmole responsible for the fluid shift. When true *hypotonic* hyponatremia occurs, treatment depends on eliminating the excess free water or suppressing the stimulus for ADH production. The rate of correction depends on the acuity with which it developed and the degree of symptomatology exhibited by the patient. Overly rapid correction can precipitate central pontine myelinolysis (CPM). In its most complete form, CPM is characterized by flaccid paralysis, dysarthria, dysphagia, and death.

Algorithm 26.2 outlines the standard treatment of hyponatremia. When the process is acute (duration of <2 days) or when severe neurologic dysfunction is present, correction of the serum [Na^+] can be 1 to 2 mEq/L/h until symptoms improve, then slowed to no more than 0.5 mEq/L/h and no more than 8 mEq/L over a 24-hour period. When the hyponatremia has been present for at least 2 days, correction should begin at no more than 0.5 mEq/L/h and no more than 6 to 8 mEq/L over a 24-hour period.

ALGORITHM 26.2 **Treatment of Hyponatremia**


Hyponatremia (<135 mEq/L)
Symptomatic OR acute (<2 days)
Asymptomatic AND chronic (>2 days)
- Treat underlying cause
- Water restriction
- Hypertonic (3%) saline to correct at rate 1-2 mEq/L/h until symptoms abate
- Calculate rate and composition of fluid by Adrogué-Madias equation (change in serum sodium by 1 L of infused fluid):
(Infused Na + K) – (serum sodium) / (TBW + 1)
- Once symptoms improve, correct serum sodium concentration at rate no more than 8 mEq/L/d
- Consider adding tolvaptan 15 mg q24 h in select circumstances
- No immediate correction needed if mild hyponatremia
- Treat underlying cause
- Water restriction
- consider sodium chloride or urea tablets
- consider loop diuretics
CORRECT AT RATE NO MORE THAN 6-8 mEq/L/d
ABBREVIATION
TBW: total body water

Most cases of hyponatremia can be corrected with free water restriction, except for those caused by true volume depletion. When more urgent correction is needed, 3% hypertonic saline can be used cautiously to raise the [Na^+]. The Adrogué-Madias equation (Box 26.1) can be used to estimate the expected change in [Na^+] after 1 L of a fluid is given; this anticipated change needs to be spread out over a number of hours to prevent overly rapid correction. However, this equation does not take into account the ongoing urinary losses and is

notoriously inaccurate. It is therefore important to be aware that there is no substitute for measuring the serum [Na^+] frequently (initially every 2 hours) to ensure a safe rate of correction.

Box 26.1 Adrogué-Madias equation

Change in [Na^+] per liter = (infusate [Na^+] + [K^+] – serum [Na^+])/(estimated total body water [kg] + 1)

Total body water = 60% of body weight

Infusate [Na^+] for selected fluids:

- 3% hypertonic saline: 513 mEq/L
- Normal (0.9%) saline: 154 mEq/L
- Ringer lactate: 130 mEq/L (+4 mEq/L of potassium)
- Half-normal (0.45%) saline: 77 mEq/L
- 5% dextrose (D5) water: 0 mEq/L

Example no. 1:

An obtunded 70-kg man presents with a serum [Na^+] of 110 mEq/L. His clinician concludes that the [Na^+] needs to be increased by 4 mEq/L in 2 hours using 3% hypertonic saline.

Expected change in [Na^+] per liter of 3% saline = (513 − 110)/(42 + 1) = 9.37 mEq/L

Amount of fluid required to achieve desired change: 4/9.37 = 0.4 L (400 mL)

Rate of infusion: 400 mL/2 h = 200 mL/h

To ensure safe rate of correction, check Na^+ frequently.

Intravenous (IV) loop diuretics can promote water excretion by blocking the maximal concentrating ability of the kidney. Sodium chloride (2-3 g bid-tid) or urea (15-30 g tid) tablets can be administered to increase the daily solute intake relative to the amount of water ingested. Each gram tablet of NaCl provides 34 mOsm of solute while 15 g of urea provides 250 mOsm of solute.

IV normal saline is effective at correcting the hyponatremia associated with true hypovolemia, as it shuts off the drive for ADH production. However, administering normal saline to a patient with SIADH would result in worsening of the hyponatremia. Here, the ADH production is fixed, and the urine osmolality is more concentrated than

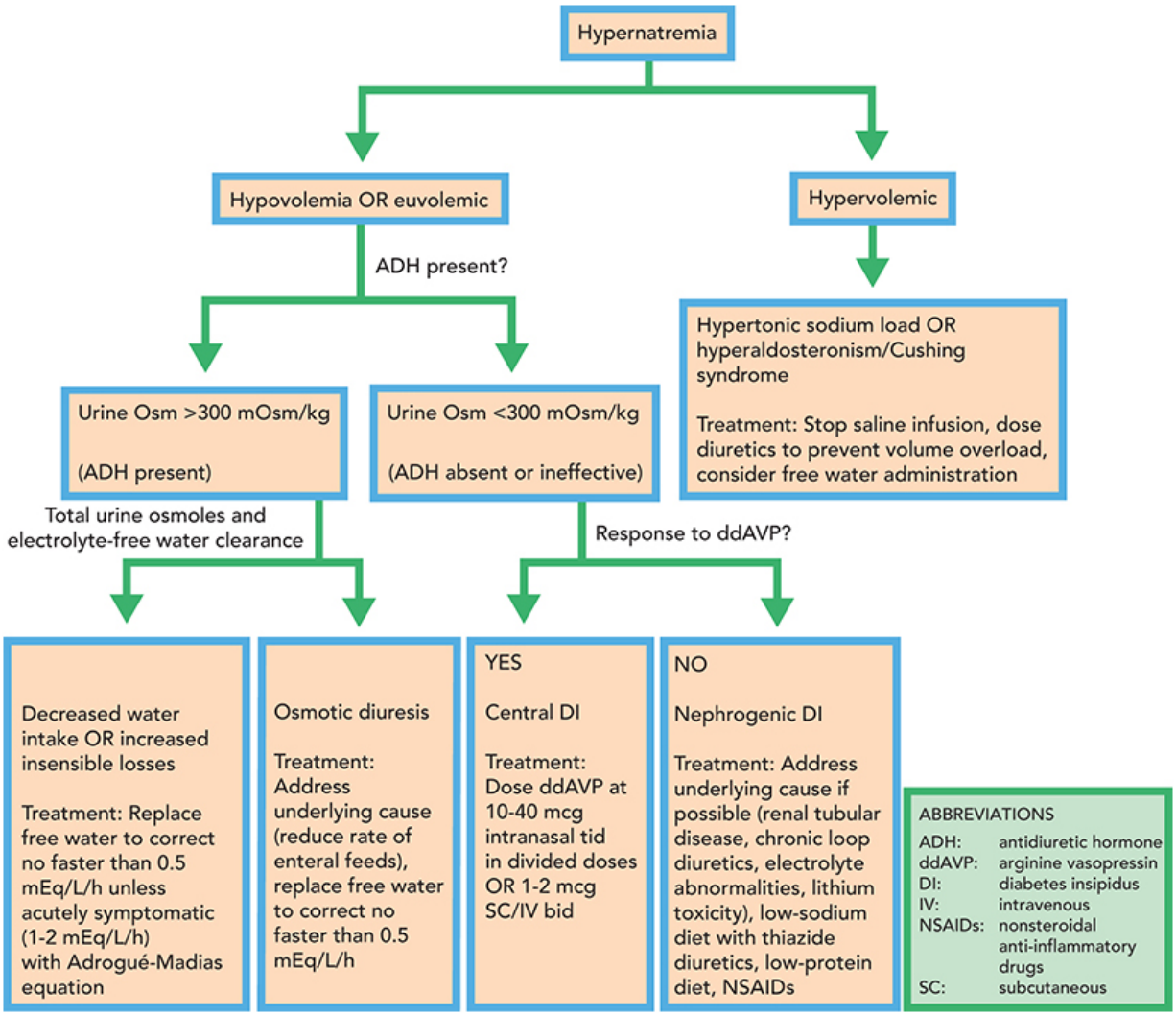
that of the fluid being administered, resulting in further dilution of the blood.

If overly rapid correction of the hyponatremia occurs within a 24-hour period, efforts must be taken to lower the serum sodium concentration into the desired range. This therapeutic relowering of the sodium can be accomplished by administering 5% dextrose in water (D5W) or desmopressin (1-2 mcg q6-8h) with continued close monitoring of the sodium concentration.

HYPERNATREMIA

Hypernatremia is almost always the result of a relative water deficit (Algorithm 26.3). The three primary mechanisms are (a) decreased free water intake, (b) increased free water loss, and (c) excessive gain of hypertonic fluid.

ALGORITHM 26.3 **Evaluation of Hypernatremia**


Hypernatremia
Hypovolemia OR euvolemic
Hypervolemic
ADH present?
Hypertonic sodium load OR hyperaldosteronism/Cushing syndrome
Treatment: Stop saline infusion, dose diuretics to prevent volume overload, consider free water administration
Urine Osm >300 mOsm/kg
(ADH present)
Urine Osm <300 mOsm/kg
(ADH absent or ineffective)
Total urine osmoles and electrolyte-free water clearance
Response to ddAVP?
Decreased water intake OR increased insensible losses
Treatment: Replace free water to correct no faster than 0.5 mEq/L/h unless acutely symptomatic (1-2 mEq/L/h) with Adrogué-Madias equation
Osmotic diuresis
Treatment: Address underlying cause (reduce rate of enteral feeds), replace free water to correct no faster than 0.5 mEq/L/h
YES
Central DI
Treatment: Dose ddAVP at 10-40 mcg intranasal tid in divided doses OR 1-2 mcg SC/IV bid
NO
Nephrogenic DI
Treatment: Address underlying cause if possible (renal tubular disease, chronic loop diuretics, electrolyte abnormalities, lithium toxicity), low-sodium diet with thiazide diuretics, low-protein diet, NSAIDs
ABBREVIATIONS
ADH: antidiuretic hormone
ddAVP: arginine vasopressin
DI: diabetes insipidus
IV: intravenous
NSAIDs: nonsteroidal anti-inflammatory drugs
SC: subcutaneous

ETIOLOGIES OF SPECIAL IMPORTANCE IN THE CRITICALLY ILL PATIENT

Decreased Water Intake

The most common etiology for hypernatremia in hospitalized patients is decreased free water intake. Although thirst is indeed a powerful stimulus, patients in certain circumstances may lack the ability to access or request water (ie, a nursing home resident or an intubated patient in the ICU). Thus, even at maximal ADH release and urinary concentration (urine osmolality >800 mOsm/kg), hypernatremia may ensue.

Insensible Free Water Loss

In ambulatory adults at room temperature, hypotonic fluid loss occurs from the skin and respiratory tract, each at a rate of approximately 400 to 500 mL/d. However, insensible water losses greatly depend on the respiratory rate, body temperature, ambient temperature, and humidity. These variables make losses much more difficult to predict in the ICU patient who may be mechanically ventilated. In general, water losses increase by 100 to 150 mL/d for each degree of body temperature more than 37 °C. Fluid losses from the skin can vary enormously with sweating or in the setting of severe burns. If these insensible losses are not matched in addition to calculated free water loss, hypernatremia will develop.

Diabetes Insipidus

The appropriate renal response to hypernatremia is the excretion of maximally concentrated urine (>800 mOsm/kg) under the control of ADH. These responses are diminished in diabetes insipidus (DI), where there is either impaired ADH secretion (central DI) or resistance to its effect at the kidney (nephrogenic DI), resulting in an inappropriately dilute urine. Central DI is typically the result of damage to the neurohypophysis (posterior pituitary) from trauma, neurosurgery, granulomatous disease, neoplasms, vascular accidents, or infection. Nephrogenic DI can be classified into disorders associated with intrinsic renal diseases of the collecting duct where ADH acts (eg, sickle cell nephropathy, polycystic kidney disease, obstructive nephropathy, Sjögren syndrome), medications (eg, lithium, demeclocycline, amphotericin, glyburide), electrolyte disorders (hypercalcemia and hypokalemia), and conditions that reduce renal medullary hypertonicity (eg, excessive water intake and the chronic use of loop diuretics).

Osmotic Diuresis

Osmotic diuresis occurs when filtered osmoles pass through the nephron, drawing out large amounts of *electrolyte-free* water into the urine. This commonly results from poorly controlled diabetes mellitus and its associated glycosuria. IV mannitol, retained uremic toxins in recovering renal failure, or high osmolar tube feeds can also result in

an osmotic diuresis. This cause of hypernatremia can resemble DI with its large urine volume but is distinguished by the high total solute excretion, typically greater than 800 to 1,000 mOsm/d. Urine osmolality is usually elevated (>300 mOsm/kg) in an osmotic diuresis compared to DI, where it is quite low.

The workup for osmotic diuresis does deserve special attention as the mechanism for the development of hypernatremia is not readily intuitive. The urinary osmolality is elevated and typically higher than that of serum osmolality. This would appear to be the proper physiologic response and might suggest that the hypernatremia will correct. However, the driving osmole in the urine is not sodium (nor its exchangeable ion, potassium), and instead, the offending osmole (eg, glucose, urea) pulls out electrolyte-free water into the urine and leaves behind an even more hypernatremic serum. The equation used to calculate this effect is the electrolyte-free water clearance, shown as follows. A positive value indicates the ongoing electrolyte-free water being excreted, which must be replaced in addition to that already lost.

$$\text{Electrolyte-free water clearance} = \text{Urine volume} \times [1 - (U_{Na+} + U_{K+})/P_{Na+}]$$

Primary Na^+ Gain

Critically ill patients often require the administration of large amounts of saline solutions such as normal saline or sodium bicarbonate during cardiopulmonary resuscitation. Normally functioning kidneys have a large capacity to excrete this excess sodium, and so iatrogenic hypernatremia is uncommon unless there is a concomitant urinary concentration defect.

TREATMENT

Hypernatremia treatment is outlined in Algorithm 26.3. The same principles as for hyponatremia apply here as well, since overly rapid correction (particularly if brain adaptation has occurred over 2 days) can result in dangerous fluid shifts. Excessive correction can result in water entering the cells, leading to cerebral edema and fatal brain

herniation. Correction should not be faster than 0.5 mEq/L/h unless acute symptoms are present or the disorder is of acute onset (<2 days), in which case correction can be 1 to 2 mEq/L/h until symptoms abate. The correction over 24 hours should not exceed 8 mEq/L.

The Adrogué-Madias equation (Box 26.2) used in correcting hyponatremia also applies to hypernatremia. The typical fluid used is 5% D5W containing no sodium, although in cases of concomitant volume depletion, normal saline should be used initially to correct the volume deficit (note that even at an infusate [Na^+] of 154 mEq/L, the serum sodium concentration would improve if it starts above this level, albeit slowly). Alternatively, one can calculate the free water deficit by the following equation. However, one must also account for the ongoing water losses (sensible and insensible) to the total amount being replaced.

$$\text{Free water deficit} = \text{Total body water} \times [(\text{Serum } [Na^+]/140) - 1]$$

Box 26.2 Adrogué-Madias equation

Change in [Na^+] per liter = (infusate [Na^+] + [K^+] − serum [Na^+])/(estimated total body water [kg] + 1)

Total body water (TBW) = 60% of body weight

Infusate [Na^+] for selected fluids:

- 3% hypertonic saline: 513 mEq/L
- Normal (0.9%) saline: 154 mEq/L
- Ringer lactate: 130 mEq/L (+4 mEq/L of potassium)
- Half-normal (0.45%) saline: 77 mEq/L
- 5% dextrose (D5) water: 0 mEq/L

Example no. 2:

A 70-kg woman presents with lassitude and a serum [Na^+] of 160 mEq/L. The replacement fluid chosen is 5% dextrose in water.

Expected change in [Na^+] per liter of 5% dextrose = (0 − 160)/(42 + 1) = −3.72 mEq/L

Over the course of 24 hours, to keep the change in sodium concentration within 8 mEq/L, each 1 L should be given over 12 hours (24-hour change −3.72 mEq/L × 2 = −7.44 mEq/L).

Rate of infusion: 1,000 mL over 12 hours = 83.3 mL/h

Note some are more familiar with the calculation of the “free water deficit.” This calculation can yield a similar answer, although it does not directly account for the rate of correction or fluid used.

Free water deficit: TBW [(serum [Na^+]/140) −1] = 42[(160/140) − 1] = 6 L

If one were to correct this to 140 mEq/L with 5% dextrose, the change in 20 mEq/L would need to occur over roughly 60 hours to avoid overly rapid correction. The total to be replaced is 6 L over 60 hours or 100 mL/h. However, this would not take into account ongoing fluid losses and may underestimate the correction; thus, frequent lab monitoring remains necessary.

Once again, equations are not precise, and one must be sure to serially check the serum [Na^+] to ensure overly rapid correction is avoided. In an osmotic diuresis, calculating the electrolyte-free water clearance can also give an estimate for the amount of water required to offset the ongoing urinary losses in addition to eliminating the offending osmole, such as metabolizing the glucose or reducing the protein content of the tube feeds.

Disorders of Volume Balance

Control of the ECF volume depends on *total body sodium* (Figure 26.2). Volume-depleted states result from total body sodium loss, while edematous states reflect total body sodium gain. As long as osmoregulatory mechanisms remain intact, the serum [Na^+] and serum osmolality remain normal.

True volume depletion, sensed by baroreceptors, results in the activation of the renin-angiotensin-aldosterone system, and the sympathetic nervous system to promote the retention of sodium and water proportionally. In more severe cases, ADH may also be recruited, resulting in water reabsorption without sodium retention and leading to hyponatremia. Urinary sodium excretion is low (often <15 mEq/L). In congestive heart failure or decompensated cirrhosis, the “effective circulating volume” is diminished, and these same responses occur. However, instead of correcting the underlying state, this excess sodium and water retention results in edema formation and ascites.

Treatment of these edematous states is often centered on addressing the underlying cause. Loop diuretics and potassium-sparing diuretics in combination with salt and water restriction can alleviate the swelling. Renal function must be followed carefully, as overzealous diuresis can precipitate a drop in the glomerular filtration rate (GFR), and this is particularly worrisome in the case of hepatorenal syndrome in decompensated cirrhosis. When advanced congestive heart failure compromises renal perfusion, diuresis may paradoxically improve renal function as cardiac performance is enhanced.

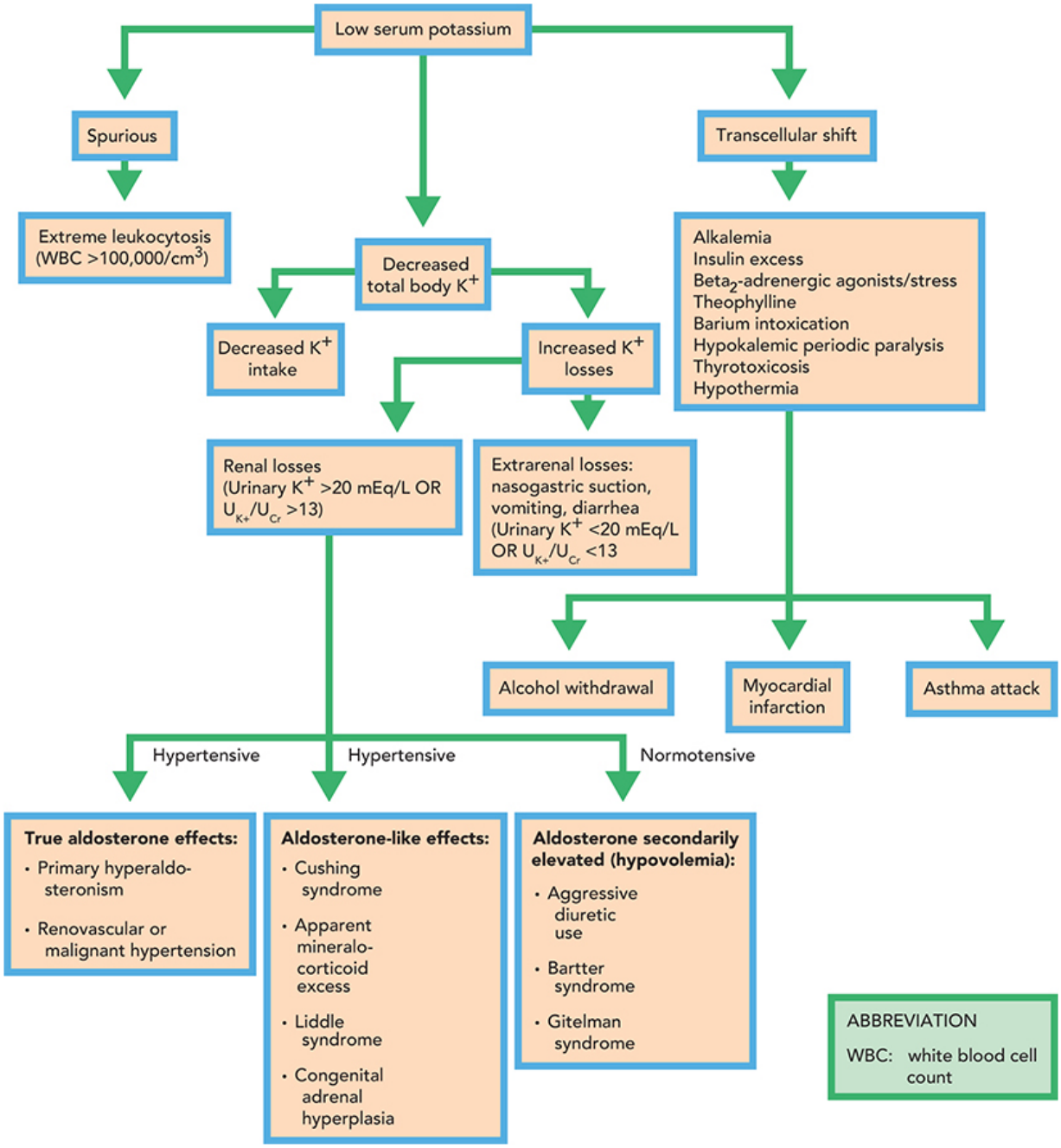
Disorders of Potassium Concentration

The total body potassium in a normal adult is approximately 3,000 to 4,000 mEq, of which 98% is intracellular. Perturbations in the serum [K^+] therefore are generally the result of transcellular shifts and do not accurately reflect the total body K^+ deficit or excess. Potassium excretion is primarily accomplished by the kidneys, at the level of the collecting duct under the influence of aldosterone. This process is coupled to sodium resorption and, therefore, volume repletion and blood pressure elevation. Aldosterone activity in the collecting duct also stimulates H^+ excretion.

HYPOKALEMIA

Hypokalemia can result from (a) shifting of potassium into cells, (b) renal wasting, or (c) extrarenal losses (Algorithm 26.4). The urinary excretion of potassium can be estimated by the ratio of urinary potassium to urinary creatinine (U_{K+}/U_{Cr}) and helps distinguish renal from extrarenal losses, although clues from the history will often suffice. The U_{K+}/U_{Cr} should be less than 13 mEq K^+/g creatinine *in the setting of hypokalemia*, reflecting renal conservation; a level greater than this suggests inappropriate renal wasting of potassium.

ALGORITHM 26.4 **Evaluation of Hypokalemia**



Symptoms of hypokalemia seldom occur unless the potassium concentration is less than 3 mEq/L, with more acute changes having greater effect. Neuromuscular fatigue, weakness, cramps, constipation, or ileus may occur and even progress to rhabdomyolysis or ascending paralysis when the potassium concentration falls to 2 mEq/L. Although the electrocardiogram (ECG) does not correlate well with [K^+], progressive changes may be seen in the individual patient.

Moderate hypokalemia may have T-wave flattening, ST-segment depression, and the appearance of U waves. Severe hypokalemia shows decreased voltage, PR interval prolongation, and QRS widening.

ETIOLOGIES OF SPECIAL IMPORTANCE IN THE CRITICALLY ILL PATIENT

Transcellular Shifts

Movement of K^+ into cells may transiently decrease the plasma [K^+] without altering total body K^+ content. The magnitude of the change is relatively small, often less than 1 mEq/L, but may exaggerate hypokalemia from other causes. Triggers of intracellular shift include alkalemia, insulin activity, and catecholamine excess. The refeeding syndrome, where nutritional support is initiated after a prolonged period of starvation, is a classic scenario where a transcellular shift exacerbates the hypokalemia in a patient with deficient stores.

Renal Wasting

Increased potassium loss by the kidney can be the result of increased urine flow (eg, loop or thiazide diuretic use, osmotic diuresis) or an elevated aldosterone state (usually with concomitant metabolic alkalosis). The presence of volume overload and hypertension suggests that the aldosterone (or aldosterone-like) effect is driving the underlying process (eg, primary hyperaldosteronism, apparent mineralocorticoid excess, Liddle syndrome). When euvolemia and normal blood pressures are present, the aldosterone effect is secondary (or reactive) in response to a volume-depleted state (eg, Bartter syndrome, Gitelman syndrome, diuretic use). Life-threatening hypokalemia can be seen in toluene intoxication (glue or paint sniffing), where its urinary metabolite hippuric acid is excreted as potassium hippurate.

Extrarenal K^+ Loss

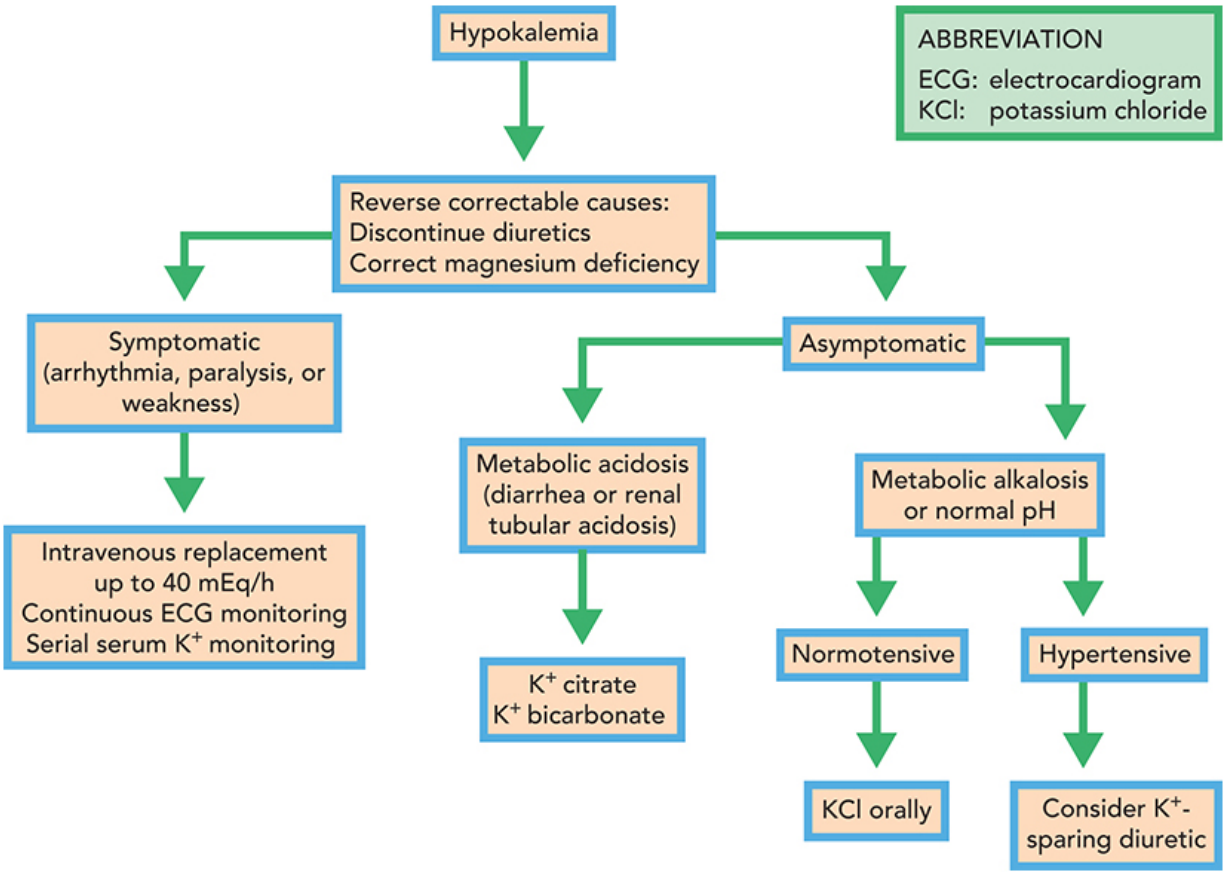
Gastrointestinal fluids (eg, saliva, stomach secretions, diarrhea) have significant K^+ content and therefore excessive enteral losses may

result in hypokalemia. Should there also be significant volume depletion, the renin-angiotensin-aldosterone system is secondarily stimulated and may ultimately result in further potassium losses in the urine. When vomiting is the primary cause, there is often a concomitant metabolic alkalosis from the acid loss. However, when diarrhea is the prominent cause, a metabolic acidosis typically prevails from the loss of bicarbonate.

TREATMENT

Treatment of hypokalemia is outlined in Algorithm 26.5. Rapid correction of hypokalemia is required when symptoms or ECG changes are present. In these cases and when patients are unable to take oral medications, IV repletion is appropriate. Otherwise, it is generally safer to correct hypokalemia via the enteral route, and larger doses can be administered orally. Potassium chloride (KCl) is typically the preparation of choice regardless of the route of administration as it promotes more rapid correction of hypokalemia and concomitant metabolic alkalosis than the other preparations. Potassium bicarbonate or citrate may be useful in cases associated with metabolic acidosis (eg, chronic diarrhea, renal tubular acidosis). Hypomagnesemia should be sought in all hypokalemic patients and corrected prior to or concurrently with K^+ repletion. A decrement of 1 mEq/L represents an estimated total body deficit of 200 to 400 mEq. However, the total body deficit is difficult to estimate accurately, and as such the serum [K^+] should be monitored frequently during therapy.

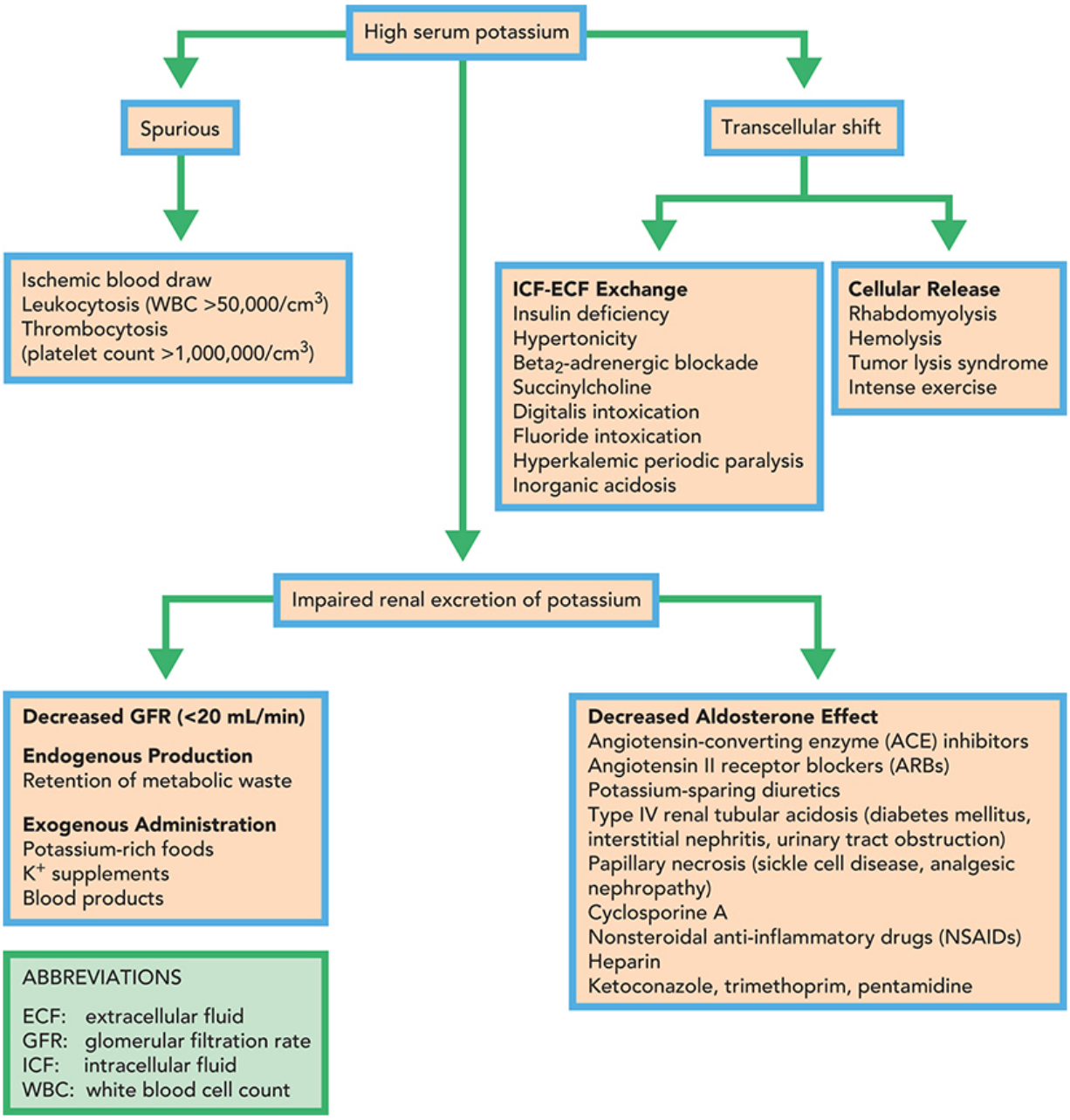
ALGORITHM 26.5 **Treatment of Hypokalemia**



HYPERKALEMIA

There are three primary mechanisms of hyperkalemia (Algorithm 26.6): (a) transcellular shifts, (b) reduced glomerular filtration, or (c) effective aldosterone deficiency. Sustained hyperkalemia almost always requires decreased renal function, as normal kidneys have a tremendous capacity for K^+ excretion. A U_{K+}/U_{Cr} value greater than 200 mEq K^+/g creatinine would be the expected renal response to hyperkalemia and values less than this would suggest a defect in renal excretion.

ALGORITHM 26.6 **Evaluation of Hyperkalemia**



Symptoms of hyperkalemia are more pronounced when acute. Neuromuscular effects may manifest as weakness that can progress to flaccid paralysis and hypoventilation. As with hypokalemia, ECG changes do not correlate well with hyperkalemia, although progressive changes are seen within the individual. Moderate hyperkalemia shows peaked T waves with increased amplitude. More severe [K^+] elevations cause prolonged PR intervals and QRS duration, atrioventricular delays, and loss of P waves. Profound hyperkalemia

causes progressive widening of the QRS complex and merging with the T wave to produce sine waves; ventricular fibrillation and asystole may ultimately occur.

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Transcellular Shifts

The movement of K^+ from the ICF to the ECF may transiently increase the plasma [K^+] without altering total body K^+ content, often amplifying the hyperkalemia resulting from other causes. Potential causes of extracellular shift include insulin deficiency, ECF hyperosmolality, inorganic acidemia, and cell breakdown (eg, rhabdomyolysis, hemolysis, tumor lysis syndrome). DKA may promote hyperkalemia through relative insulin deficiency, despite the presence of total body potassium depletion. Medications that cause extracellular shifts include nonselective beta-blockers, digitalis, and succinylcholine. The hyperkalemia that occurs with succinylcholine is usually small (0.5 mEq/L) and brief (resolving within 10-15 minutes), but it can be significantly accentuated in patients with massive trauma, burns, or neuromuscular disease.

Reduced Glomerular Filtration

A reduced GFR in both acute and chronic kidney disease can predispose to the development of hyperkalemia. Diseased kidneys respond to progressive insufficiency with increased potassium excretion per functioning nephron. This compensation is typically adequate until the GFR falls to the point of oliguria. Thus, when hyperkalemia develops in a nonoliguric patient, there is usually a second contributing mechanism or the renal injury is severe and acute. Diminished distal tubular sodium delivery, as occurs in volume depletion (prerenal azotemia), is a common contributing mechanism in the critically ill patient. Patients with underlying chronic kidney disease already have decreased functioning nephron mass, and any further decrease in GFR can predispose to the development of hyperkalemia.

Effective Aldosterone Deficiency

Medications can account for the relative hypoaldosterone state that contributes to hyperkalemia in the ICU patient. Heparin, ketoconazole, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) decrease aldosterone production. Spironolactone and eplerenone are competitive aldosterone antagonists, while amiloride, triamterene, trimethoprim, and pentamidine block sodium resorption (and thus potassium excretion) at the collecting duct where aldosterone would exert its effect. NSAIDs inhibit renin secretion, a process that is several steps upstream of aldosterone release; these medications can also decrease glomerular filtration in volume-depleted states through the inhibition of local vasodilatory prostaglandins.

TREATMENT

Hyperkalemia treatment is outlined in Table 26.1. The presence of symptoms or ECG changes associated with hyperkalemia necessitates the prompt initiation of measures capable of rapidly lowering the serum [K^+]. Calcium serves to stabilize the cardiac myocyte membrane but does not actually reduce the [K^+]; therefore, it is given simultaneously with other therapies that shift potassium into the cell (insulin and albuterol) and promote its excretion (sodium zirconium cyclosilicate, potassium-wasting diuretics, and hemodialysis). The use of sodium bicarbonate to shift potassium intracellularly has fallen out of favor given its comparatively weak effect in the absence of an inorganic metabolic acidosis. Dialytic therapies are generally reserved for cases of severe hyperkalemia not responsive to medical management.

TABLE 26.1 Acute Therapies for the Management of Hyperkalemia

Treatment	Dosing	Onset/Duration	Magnitude of [K+] Decline	Comments

Treatment	Dosing	Onset/Duration	Magnitude of [K+] Decline	Comments
Ca^{2+}	1 g of 10% calcium gluconate or calcium chloride infused IV over 2-3 min; may repeat if no improvement in ECG by 5 min	Immediate onset, lasting 30-60 min	None	Calcium chloride should be administered via a central vein to decrease risk of extravasation and skin necrosis.
Insulin	10 units of regular insulin IV (with one ampule of D50 IV if not significantly hyperglycemic)	Onset at 15 min, lasting 6-8 h	~1 mEq/L	Watch for hypo- or hyperglycemia (if dextrose given); the latter can offset insulin's K^+-lowering effect.
Albuterol	10-20 mg given by nebulized inhalation over 15 min OR 0.5 mg in 100 mL of 5% dextrose infused IV over 15 min	Onset at 10-30 min, lasting 3-6 h	1-1.5 mEq/L	Tachycardia and variable effects on blood pressure may result; hyperglycemia may worsen and offset some K^+-lowering effect.

Treatment	Dosing	Onset/Duration	Magnitude of [K+] Decline	Comments
$NaHCO_3$	2-4 mEq/min in drip (3 ampules $NaHCO_3$ in sterile water or 5% dextrose) until bicarbonate normalized	Onset at 4 h, lasting >6 h	0.5-0.75 mEq/L	Not effective unless concurrent inorganic metabolic acidosis; watch for volume overload and may lower serum ionized $[Ca^{2+}]$ and make more susceptible to arrhythmias
Loop +/– thiazide diuretics	Widely variable dose depends on GFR.	Onset at 30-60 min, lasting 4-6 h (duration prolonged in renal insufficiency)	Variable depending on diuretic response	Avoid in volume-depleted states until euvolemia restored
Sodium zirconium cyclosilicate	10 g orally tid for up to 48 h	Onset may be as early as 1-2 h, with established effect at 48 h.	0.7 mEq/L at 48 h	Caution with use in patients with gastrointestinal motility disorders; watch for worsening volume overload from sodium content.

Treatment	Dosing	Onset/Duration	Magnitude of [K+] Decline	Comments
Hemodialysis	Variable, based on starting [K^+]	Immediate onset, lasting until dialysis completion	Variable, based on dialysis dose and dialysate [K^+]	Watch for posttreatment K^+ rebound beginning immediately after dialysis completion.

ECG, electrocardiogram; GFR, glomerular filtration rate; IV, intravenous.

Another important component of therapy is to limit exogenous potassium intake. Each 8-oz can of high-protein tube feeds contains approximately 10 mEq of K^+, and a single unit of packed red blood cells with a prolonged storage time may contribute approximately 5 mEq.

Disorders of Calcium Concentration

The extracellular calcium concentration is tightly maintained and reflects the coordinated action of multiple hormones: parathyroid hormone (PTH), 1,25-$(OH)_2$ vitamin D (calcitriol), and to a lesser extent calcitonin. Approximately 99% of body calcium is in bone, with most of the remaining 1% in the ECF. The total plasma calcium concentration consists of three fractions:

- Approximately 45% circulates as the physiologically active ionized (or free) calcium.
- Approximately 40% is bound to albumin, with greater binding in alkalemia.
- The remaining 15% is bound to multiple organic and inorganic anions such as sulfate, phosphate, lactate, and citrate.

The ionized Ca^{2+} concentration, which must be maintained within a narrow range (4.6-5.1 mg/dL) for optimal neuromuscular function, is under exquisitely tight minute-to-minute control by PTH. PTH increases serum [Ca^{2+}] by stimulating bone resorption, calcium reclamation by the kidney, and renal conversion of 25-OH vitamin D to its more active form, 1,25-$(OH)_2$ vitamin D, which then promotes intestinal calcium absorption (Figure 26.3). 1,25-$(OH)_2$ vitamin D in turn inhibits the production and secretion of PTH, closing the feedback loop.

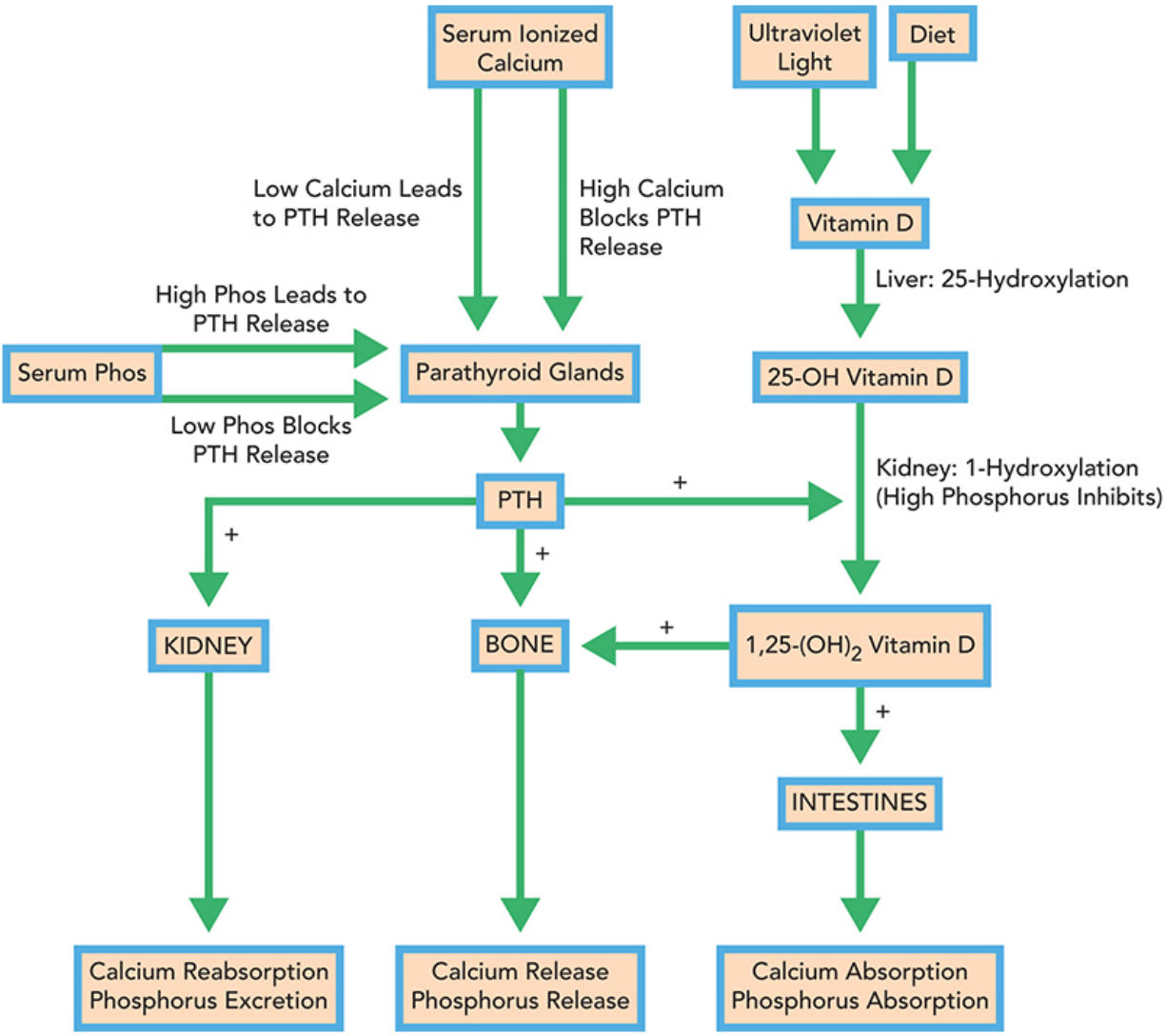


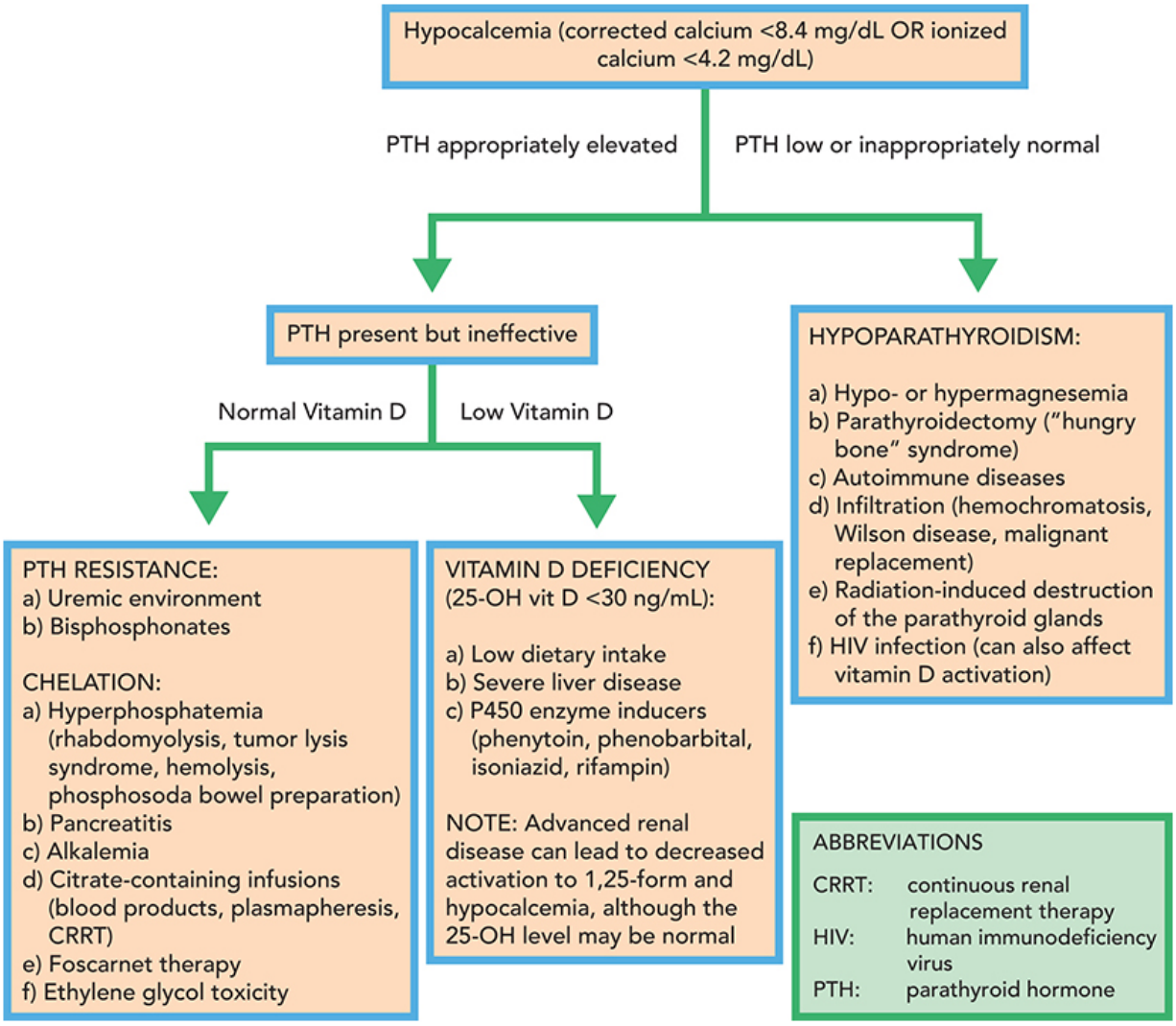
FIGURE 26.3 **Regulation of calcium and phosphorus**. PTH, parathyroid hormone.

Disorders of [Ca^{2+}] are common among critically ill patients. Low ionized [Ca^{2+}] has been observed in up to 88% of ICU patients. Furthermore, the presence of hypocalcemia serves as a marker of disease severity and patient mortality.

HYPOCALCEMIA

Since the vast majority of calcium is stored in bone, hypocalcemia (corrected calcium <8.4 mg/dL or ionized calcium <4.2 mg/dL) reflects a defect in the transfer of calcium into the ECF (Algorithm 26.7). Evaluation of such disorders always starts with measuring the PTH level, which should be elevated (even levels in the "normal" range are inappropriate in the setting of hypocalcemia). If the PTH level is appropriately elevated, then there is resistance to its function at the level of bone, inadequate vitamin D activity, or chelation of the calcium from the circulation.

ALGORITHM 26.7 **Evaluation of Hypocalcemia**


Hypocalcemia (corrected calcium <8.4 mg/dL OR ionized calcium <4.2 mg/dL)
PTH appropriately elevated
PTH low or inappropriately normal
PTH present but ineffective
Normal Vitamin D
Low Vitamin D
HYPOPARATHYROIDISM:
a) Hypo- or hypermagnesemia
b) Parathyroidectomy ("hungry bone" syndrome)
c) Autoimmune diseases
d) Infiltration (hemochromatosis, Wilson disease, malignant replacement)
e) Radiation-induced destruction of the parathyroid glands
f) HIV infection (can also affect vitamin D activation)
PTH RESISTANCE:
a) Uremic environment
b) Bisphosphonates
CHELATION:
a) Hyperphosphatemia (rhabdomyolysis, tumor lysis syndrome, hemolysis, phosphosoda bowel preparation)
b) Pancreatitis
c) Alkalemia
d) Citrate-containing infusions (blood products, plasmapheresis, CRRT)
e) Foscarnet therapy
f) Ethylene glycol toxicity
VITAMIN D DEFICIENCY (25-OH vit D <30 ng/mL):
a) Low dietary intake
b) Severe liver disease
c) P450 enzyme inducers (phenytoin, phenobarbital, isoniazid, rifampin)
NOTE: Advanced renal disease can lead to decreased activation to 1,25-form and hypocalcemia, although the 25-OH level may be normal
ABBREVIATIONS
CRRT: continuous renal replacement therapy
HIV: human immunodeficiency virus
PTH: parathyroid hormone

Symptoms of hypocalcemia include circumoral or distal paresthesias and tetany. Latent tetany may be induced through several maneuvers. Trousseau sign is positive when carpal spasm is induced after inflating a blood pressure cuff around the arm above systolic pressure for 3 minutes. Chvostek sign is present when perioral muscle twitching is elicited with tapping the area of the facial nerve anterior to the ear. Acute, severe hypocalcemia may present with confusion, seizures, or bradycardia. ECG findings include QT interval prolongation, bradycardia, or complete heart block.

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Pseudohypocalcemia

Approximately 45% of serum Ca^{2+} exists in its free ionized form. Changes in serum albumin and serum anions alter total measured serum [Ca^{2+}] without affecting the clinically relevant ionized [Ca^{2+}]. Hypoalbuminemia is very common in the ICU setting because albumin concentrations fall with a systemic inflammatory response and with large-volume fluid resuscitation. The total measured serum [Ca^{2+}] is lowered in such situations, but the ionized [Ca^{2+}] remains within the normal range. It is recommended that the ionized [Ca^{2+}] always be measured in this setting, since the equation for correction (adding back 0.8 mg/dL to the measured calcium for each 1 mg/dL drop in albumin from 4 mg/dL) may not correlate well.

Chelation

An increase in the availability of any anion that combines readily with Ca^{2+} may cause hypocalcemia, as ionized Ca^{2+} is chelated. The release of negatively charged fatty acids in severe pancreatitis or the spillage of large amounts of phosphate in rhabdomyolysis or hemolysis can result in hypocalcemia. Tremendous deposition into bone after parathyroidectomy is termed the “hungry bone” syndrome and can persist for months. Chelation by citrate-containing fluids, such as blood products in massive transfusions or anticoagulants in some forms of continuous dialysis and plasmapheresis, can be seen in critically ill patients.

Sepsis

Hypocalcemia occurs commonly in sepsis, particularly when involving a gram-negative organism. The pathogenesis is incompletely understood, but most patients have elevated PTH and low calcitriol levels. Elevated levels of procalcitonin have been found in many of these patients, suggesting that this hormone precursor may exert a hypocalcemic effect in the critically ill population.

TREATMENT

The management of symptomatic hypocalcemia or that associated with ECG abnormalities should be prompt and aggressive. IV Ca^{2+} replacement should be initiated in such situations. Treatment is outlined in Table 26.2.

TABLE 26.2 Treatment of Hypocalcemia

General guidelines of therapy:

1. If ECG changes or symptoms present, begin IV replacement:
   a. Consider early initiation of hemodialysis when caused by hyperphosphatemia.
   b. Bolus 2 g $MgSO_4$ IV over 15 min if known hypomagnesemia or empirically if renal function is normal.
   c. Bolus 2 g calcium gluconate (20 mL or 2 ampules of 10% calcium gluconate; 1 g = 93 mg elemental Ca^{2+}) in 50-100 mL of 5% dextrose or saline IV over 10-15 min.
   d. Begin continuous Ca^{2+} infusion: dilute 6 g of calcium gluconate[a] in 500 mL of 5% dextrose or saline and infuse at 0.5-1.5 mg elemental Ca^{2+}/kg/h.
   e. Follow ionized [Ca^{2+}] or corrected [Ca^{2+}] q6h and continue infusion until [Ca^{2+}] normalizes.
   f. Overlap with PO replacement.
2. Dose 1-2 g elemental Ca^{2+} PO tid to qid, separate from meals.
3. Can add 0.25-4 mcg/d calcitriol AND/OR ergocalciferol especially in vitamin D–deficient states
4. Can add sodium restriction and hydrochlorothiazide if hypercalciuria occurs

[a]Alternatively, can use 2 g, 20 mL, or 2 ampules of 10% calcium chloride (1 g = 272 mg elemental Ca^{2+}) but should only be administered through a central vein.
ECG, electrocardiogram; IV, intravenous; PO, by mouth.

Hypomagnesemia, if present, must be treated first for effective correction, as severe depletion of this electrolyte can impair PTH release. If the cause of low [Ca^{2+}] is marked hyperphosphatemia, it is important to limit calcium replacement to those cases in which cardiac and neurologic symptoms are significant, since overaggressive correction may result in metastatic calcification. In cases of profound

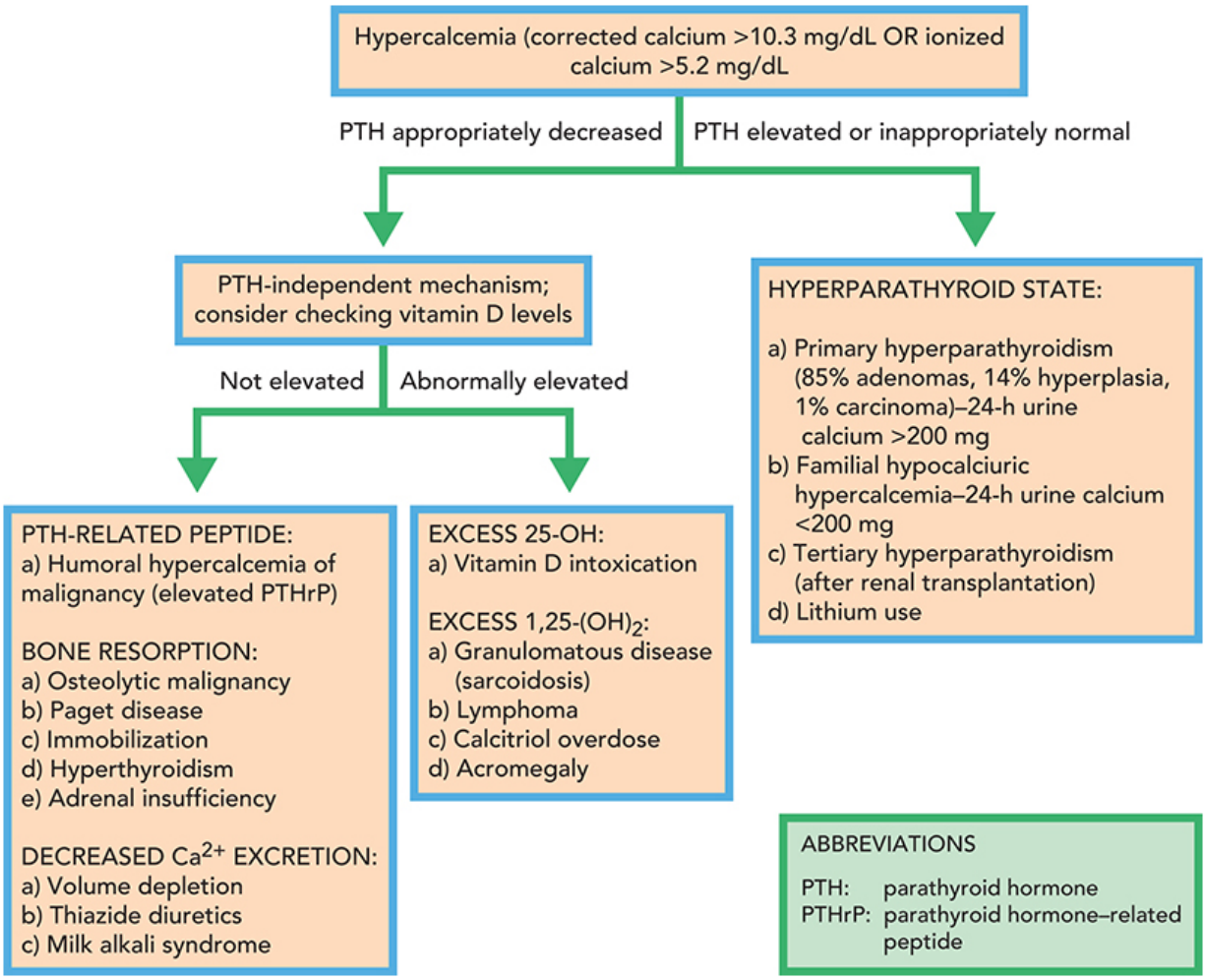
hypocalcemia, clearance of the chelating species through the early initiation of hemodialysis with higher Ca^{2+} dialysate should be considered. For hypocalcemia occurring in the setting of profound sepsis or other shock states, therapy-guiding evidence is lacking. Although increases in cardiac contractility and blood pressure have been observed by Ca^{2+} administration, some animal data suggest reperfusion injury and mortality may be worsened.

Asymptomatic hypocalcemia may be managed with oral calcium supplements along with vitamin D or its active metabolite calcitriol to increase intestinal absorption. Supplemental calcium should be administered between meals and away from other medications (particularly thyroid hormone and iron) to maximize absorption.

HYPERCALCEMIA

As with hypocalcemia, hypercalcemic disorders (corrected calcium >10.3 mg/dL or ionized calcium >5.2 mg/dL) are first evaluated by determining the PTH status (Algorithm 26.8). Levels should be maximally suppressed, and thus, even "normal" levels are inappropriately high, suggesting a hyperparathyroid state. If the PTH level is indeed suppressed, hypercalcemia can still result from nutritional vitamin D overdose or excess formation of 1,25-$(OH)_2$ vitamin D (sarcoidosis, granulomatous disease, or lymphoma). Malignancy can lead to hypercalcemia through production of a PTH-like substance (PTH-related peptide, PTHrP) or lytic destruction of bone with release of calcium into the circulation.

ALGORITHM 26.8 **Evaluation of Hypercalcemia**



Symptoms of hypercalcemia can occur at levels greater than 12 mg/dL and tend to be more severe with rapid elevations. Polyuria is common, resulting in a volume-depleted state through the action of calcium at the loop of Henle. Gastrointestinal symptoms are also frequently seen, with anorexia, constipation, and abdominal pain, with pancreatitis a rare secondary complication. Neurologic symptoms include weakness, fatigue, confusion, stupor, or coma. The ECG may reveal a shortened QT interval or variable degrees of atrioventricular block.

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Humoral Hypercalcemia of Malignancy

Certain malignancies, particularly squamous cell lung cancer, cancers of the head and neck, esophagus, genitourinary tract, and pheochromocytomas may produce a hormone that differs from PTH but retains its biologic activity. This PTHrP is not detected by standard PTH measurements and must be ordered separately when suspected. In most cases of humoral hypercalcemia of malignancy, patients have advanced disease.

Osteolytic Hypercalcemia of Malignancy

In this separate form of cancer-associated hypercalcemia, cytokines produced by tumor cells stimulate osteoclast bone resorption. Hypercalcemia and hyperphosphatemia occur with extensive bone involvement by tumor, and the serum alkaline phosphatase is often significantly elevated. The PTH is appropriately suppressed. The most frequently associated malignancies include breast carcinoma, non–small cell lung cancer, myeloma, and lymphoma.

Excess Calcitriol Production

Excess unregulated vitamin D activation can be produced by granulomatous disease such as sarcoidosis as well as the lymphocytes of some Hodgkin and non-Hodgkin lymphomas. These cells possess intrinsic 1-alpha hydroxylase activity, leading to excessive calcitriol production. The elevation in $[Ca^{2+}]$ is usually less severe than in humoral hypercalcemia of malignancy.

Immobilization

Complete bed rest can result in hypercalcemia after several days. There is increased osteoclast activity as well as diminished bone formation, with resultant hypercalcemia. It is usually more severe when renal function is impaired. Remobilization, when possible, leads to improvement and eventual resolution of the hypercalcemia.

TREATMENT

Hypercalcemia treatment is outlined in Table 26.3. Rapidly acting therapies for hypercalcemia are warranted if severe symptoms are

present or with [Ca^{2+}] greater than 12 mg/dL. First, hypovolemia should be corrected with IV isotonic fluid boluses. Continuing maintenance IV saline after achieving euvolemia further promotes calcium excretion. Loop diuretics are generally avoided in the early stages of correction as they may prevent adequate volume restoration. However, they are useful if signs of hypervolemia develop. Calcitonin can also lower the serum [Ca^{2+}] within hours, and hemodialysis against a low calcium dialysate bath can be used if other medical maneuvers are unsuccessful.

TABLE 26.3 Treatment of Hypercalcemia

Treatment	Dosing	Onset/Duration	Comments
Isotonic saline	Bolus isotonic saline until euvolemic (may require up to 3-4 L), then adjust rate to achieve urine output of 100-150 mL/h	Onset at 2-4 h	Watch for signs of volume overload; loop diuretics may help with calcium excretion, but should be held until volume deficits have first been corrected.
Calcitonin	4-8 IU/kg IM or SC q6-12h	Onset at 4-6 h; tachyphylaxis develops after 2-3 d.	Lowers serum Ca^{2+} 1-2 mg/dL; side effects include flushing, nausea, and, rarely, allergic reactions.
Bisphosphonates	Zoledronate 4 mg IV over 15 min OR pamidronate 60-90 mg IV over 2-4 h	Onset at 2 d with peak effect at 4-6 d; lasts 2-4 wk.	Decrease infusion rate of pamidronate or lower zoledronate dose in renal insufficiency.

Treatment	Dosing	Onset/Duration	Comments
Denosumab	60-120 mg SC	Onset within 3 d, half-life of 25 d	Watch for hypocalcemia, risk for infection.
Glucocorticoids	Prednisone 20-60 mg/d (or equivalent glucocorticoid dose)	Onset in 5-10 d	Effective only in cases of granulomatous disease and hematologic malignancies
Hemodialysis	Variable based on starting [Ca^{2+}]	Immediate onset, lasting until dialysis completion	Useful for cases of severe hypercalcemia (>16 mg/dL) and when diuretic-resistant volume overload prohibits saline administration
General guidelines of therapy: 1. Correct volume depletion FIRST, with isotonic normal saline. 2. If ECG changes or severe symptoms are present, begin the most rapidly acting therapies in combination. 3. If rapid improvement is not seen (or anticipated due to the underlying condition), consider adding the longer-acting treatments (bisphosphonates) early since their effects are delayed.			

ECG, electrocardiogram; IM, intramuscular; IV, intravenous; SC, subcutaneous.

While initiating the acute therapies, it is often necessary to simultaneously start long-term measures of Ca^{2+} control. Usually, this consists of administering an IV bisphosphonate, which decreases Ca^{2+} resorption from bone by osteoclasts. In situations of calcitriol excess and when hypercalcemia occurs as a result of hematologic

malignancies, the administration of glucocorticoids is effective for lowering the serum [Ca^{2+}] and can be used alone or with bisphosphonates. Denosumab has been used to treat hypercalcemia related to malignancy; it is a monoclonal antibody to the receptor activator of nuclear factor kappa B ligand (RANKL), inhibiting its interaction with RANK on the surface of osteocytes, resulting in decreased osteoclast differentiation. A potential side effect is symptomatic hypocalcemia, which is more pronounced in patients with renal insufficiency and a creatinine clearance less than 30 mL/min.

Disorders of Phosphorus Concentration

Approximately 85% of total body phosphorus (as PO_4^{3-}) is in bone, and most of the remainder is within cells as the major intracellular anion. As only 1% of total body phosphorus is in the ECF, the serum PO_4^{3-} concentration may not reflect total body phosphorus stores. In addition to its importance in bone formation, phosphorus is an integral component of adenosine triphosphate (ATP) and thus critical for normal cellular metabolism. Furthermore, its presence in the red blood cell as 2,3-bisphosphoglycerate makes it important in the regulation of hemoglobin oxygen affinity and therefore tissue oxygen delivery.

Phosphorus balance is determined primarily by fibroblast growth factor 23 (FGF23), but also by PTH, active vitamin D (calcitriol), and insulin. PTH lowers [PO_4^{3-}] through urinary excretion. Calcitriol increases [PO_4^{3-}] by enhancing intestinal phosphorus absorption. FGF23 is a hormone produced by osteocytes with a primary function of increasing phosphorus excretion by the kidney. It is stimulated by hyperphosphatemia, PTH, and calcitriol and in turn closes these feedback loops by inhibiting PTH production and by decreasing vitamin D activation. FGF23 has been shown to have off-target effects on cardiac remodeling and may in part be responsible for left ventricular hypertrophy seen in chronic kidney disease and hyperphosphatemia, where levels are chronically elevated. Finally, insulin lowers serum levels by shifting PO_4^{3-} into cells.

Hypophosphatemia is common in acutely ill patients, having been found to occur in 29% of surgical ICU patients. Hyperphosphatemia is frequently encountered in patients with renal failure.

Since many of the regulators of phosphorus are the same as those involved in calcium homeostasis, there is considerable overlap in the maintenance of an appropriate balance. In order to adequately assess phosphorus disorders, one must take into account the concurrent calcium concentration. This is summarized in Table 26.4 for the more common etiologies.

TABLE 26.4 Interpretation of Serum Calcium and Phosphorus Values

Ca^{2+}	PO_4^{3-}	PTH	Diagnosis
↑	↓	↑	Primary hyperparathyroidism
↑	↓	↓	Humoral hypercalcemia
↑	↑	↓	Osteolytic malignancy (myeloma)
↑	↑	↓	Vitamin D excess, granulomas, lymphomas
↓	↑	↓	Hypoparathyroidism, Mg^{2+} disorders
↓	↑	↑	PTH resistance (pseudohypoparathyroidism)
↓	↑	↑	CKD (secondary hyperparathyroidism)
↓	↓	↑	Severe vitamin D deficiency

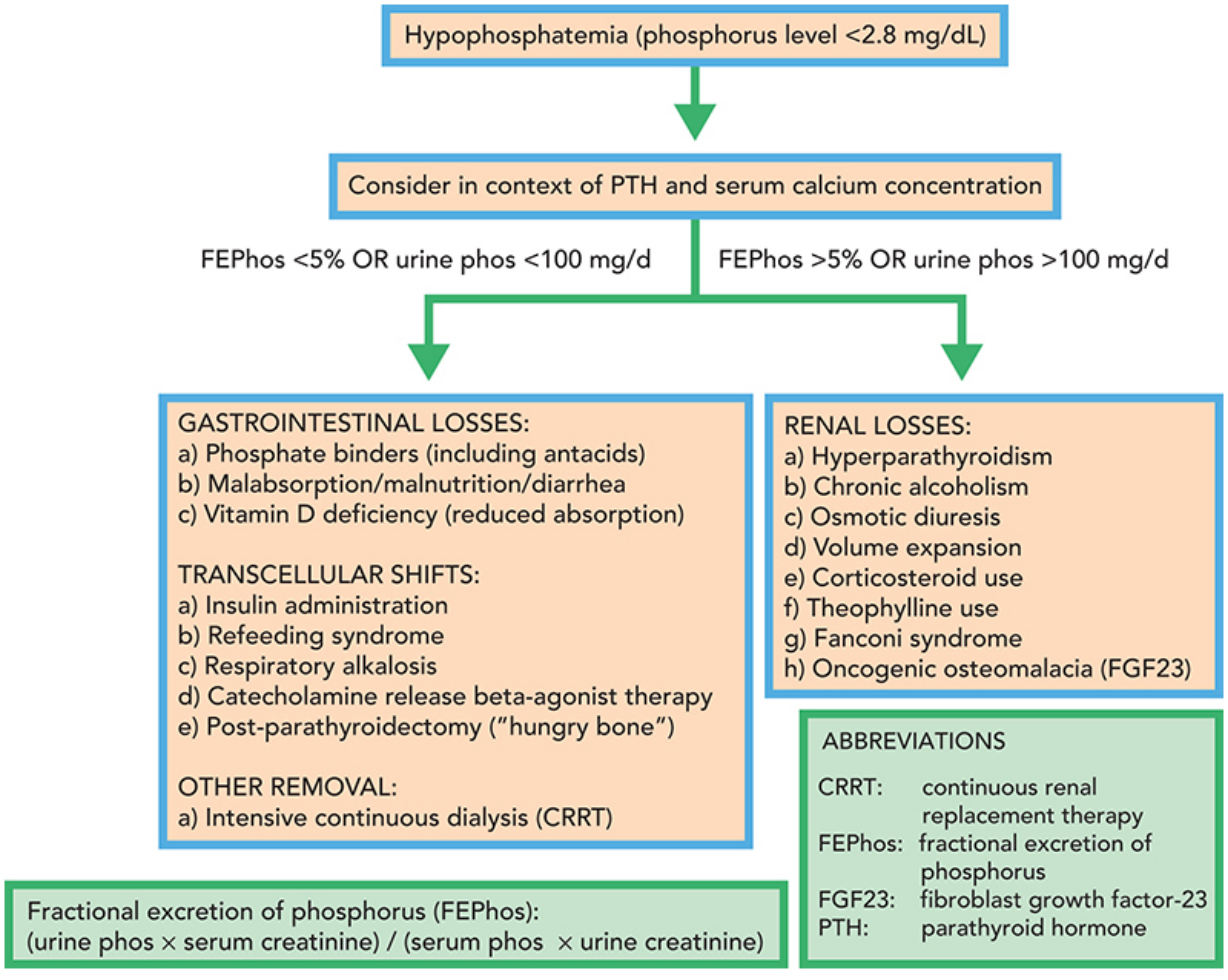
CKD, chronic kidney disease; PTH, parathyroid hormone.

HYPOPHOSPHATEMIA

When evaluating a patient with hypophosphatemia, one should first rule out severe vitamin D deficiency and primary hyperparathyroidism (Algorithm 26.9). The remaining causes include gastrointestinal losses (eg, phosphate binders, malnutrition, diarrhea), transcellular shifts (eg,

insulin, refeeding syndrome, respiratory alkalosis), or renal wasting. Losses by the kidney can be distinguished by the finding of a high fractional excretion of phosphorus (suggested by value >5%), an inappropriate response to the prevailing hypophosphatemia. An elevated fractional excretion of phosphorus is associated with the conditions of hyperparathyroidism, vitamin D deficiency, or tubular defects. Continuous renal replacement modalities used in the ICU setting can dramatically deplete serum phosphorus levels and require close monitoring.

ALGORITHM 26.9 Evaluation of Hypophosphatemia


Hypophosphatemia (phosphorus level <2.8 mg/dL)
Consider in context of PTH and serum calcium concentration
FEPhos <5% OR urine phos <100 mg/d
FEPhos >5% OR urine phos >100 mg/d
GASTROINTESTINAL LOSSES:
a) Phosphate binders (including antacids)
b) Malabsorption/malnutrition/diarrhea
c) Vitamin D deficiency (reduced absorption)
TRANSCELLULAR SHIFTS:
a) Insulin administration
b) Refeeding syndrome
c) Respiratory alkalosis
d) Catecholamine release beta-agonist therapy
e) Post-parathyroidectomy ("hungry bone")
OTHER REMOVAL:
a) Intensive continuous dialysis (CRRT)
RENAL LOSSES:
a) Hyperparathyroidism
b) Chronic alcoholism
c) Osmotic diuresis
d) Volume expansion
e) Corticosteroid use
f) Theophylline use
g) Fanconi syndrome
h) Oncogenic osteomalacia (FGF23)
ABBREVIATIONS
CRRT: continuous renal replacement therapy
FEPhos: fractional excretion of phosphorus
FGF23: fibroblast growth factor-23
PTH: parathyroid hormone
Fractional excretion of phosphorus (FEPhos):
(urine phos × serum creatinine) / (serum phos × urine creatinine)

Symptoms typically occur only when there is total body PO_4^{3-} depletion and the serum [PO_4^{3-}] is less than 1 mg/dL. Muscular

weakness (including the diaphragm) can be seen, while paresthesias, seizures, stupor, or coma may develop when severe.

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Intracellular Shift

Respiratory alkalosis is a very common cause of redistributive hypophosphatemia as the intracellular rise in pH stimulates glycolysis and the subsequent phosphorylation of various intermediates in the pathway. The marked anabolism that occurs during the abrupt reversal of negative caloric states with dextrose-containing IV fluids or total parenteral nutrition (refeeding syndrome) similarly shifts PO_4^{3-} to the ICF and can occur after as little as 2 days of nutritional restriction. The accompanying surge in insulin further promotes the intracellular translocation of phosphorus.

Renal Wasting

Hyperparathyroidism from any cause can increase renal PO_4^{3-} excretion. Chronic alcohol consumption also causes renal PO_4^{3-} wasting by an unknown mechanism. This, in combination with the usually poor nutritional status of these patients, contributes to a total body PO_4^{3-} deficit. Furthermore, the respiratory alkalosis of liver failure, the increased adrenergic tone of withdrawal, and the refeeding syndrome occurring with dextrose infusions can all lead to profound hypophosphatemia in the hospitalized patient with chronic alcohol ingestion.

Increased renal tubular fluid flow from any cause can also lead to urinary PO_4^{3-} wasting. This can be seen with aggressive volume expansion or with osmotic diuresis, such as that which occurs with the glycosuria of DKA. Furthermore, insulin therapy in the management of DKA shifts PO_4^{3-} into cells and may worsen the hypophosphatemia.

Oncogenic osteomalacia involves tumor production of FGF23. An integral part of normal phosphorus homeostasis, FGF23 can lead to

renal phosphorus wasting when overproduced through nonregulated ectopic production from tumors.

Continuous Hemodialysis

Standard intermittent hemodialysis is only able to inefficiently remove phosphorus from the intravascular space and thus rarely leads to hypophosphatemia on its own. However, with continuous hemodialysis modalities, there is a state of constant negative efflux that can result in significant hypophosphatemia. Patients on continuous renal replacement therapy (CRRT) should have their phosphorus levels checked every 12 to 24 hours, and if hypophosphatemia develops, standard treatment measures should be employed.

TREATMENT

Hypophosphatemia treatment is outlined in Table 26.5. Mild hypophosphatemia (1.9-2.5 mg/dL) is common in the hospitalized patient and is often simply caused by transcellular shifts, requiring no specific treatment except correction of the underlying cause. Severe, symptomatic hypophosphatemia (<1.0 mg/dL), however, may require IV PO_4^{3-} therapy. Although the rapid administration of large doses of IV PO_4^{3-} (0.8 mmol/kg over 30 minutes) to critically ill patients has been shown to be safe and effective, care must be taken with parenteral therapy to avoid hyperphosphatemia, which may lead to hypocalcemia and metastatic calcification. In the presence of renal insufficiency, IV PO_4^{3-} should be given at lower doses (33% of usual doses in severe renal failure) and with even greater care. IV repletion can be transitioned to oral therapy when the [PO_4^{3-}] is greater than 1.5 mg/dL. Enteral replacement may result in nausea and diarrhea. Due to the need to replenish intracellular stores, 24 to 36 hours of repletion may be required. There has been no demonstrated clear benefit to aggressive repletion of PO_4^{3-} in asymptomatic hypophosphatemia. Studies of PO_4^{3-} therapy in the treatment of DKA, for instance, have shown no improved outcomes and may even suggest increased morbidity, primarily through resultant hypocalcemia.

TABLE 26.5 Treatment of Hypophosphatemia

1. If symptomatic, or intolerant to PO, begin IV replacement (reduce doses in setting of renal insufficiency):
   a. Severe (≤1 mg/dL): dose 0.6 mmol/kg IBW IV[a] over 6 h; if hypotension ensues, suspect hypocalcemia and discontinue infusion.
   b. Moderate (1-1.8 mg/dL): dose 0.4 mmol/kg IBW IV[a] over 6 h
   c. Mild (1.9-2.5 mg/dL): dose 0.2 mmol/kg IBW IV[a] over 6 h
2. If asymptomatic, dose 0.5-1 g elemental phosphorus PO bid-tid
   a. Neutra-phos: 250 mg (8 mmol) phosphorus and 7 mEq each of Na^+ and K^+
   b. Neutra-phos K: 250 mg phosphorus and 14 mEq K^+
   c. K-phos neutral: 250 mg phosphorus with 13 mEq Na^+ and 1.1 mEq K^+
   d. Treat vitamin D deficiency, if present.

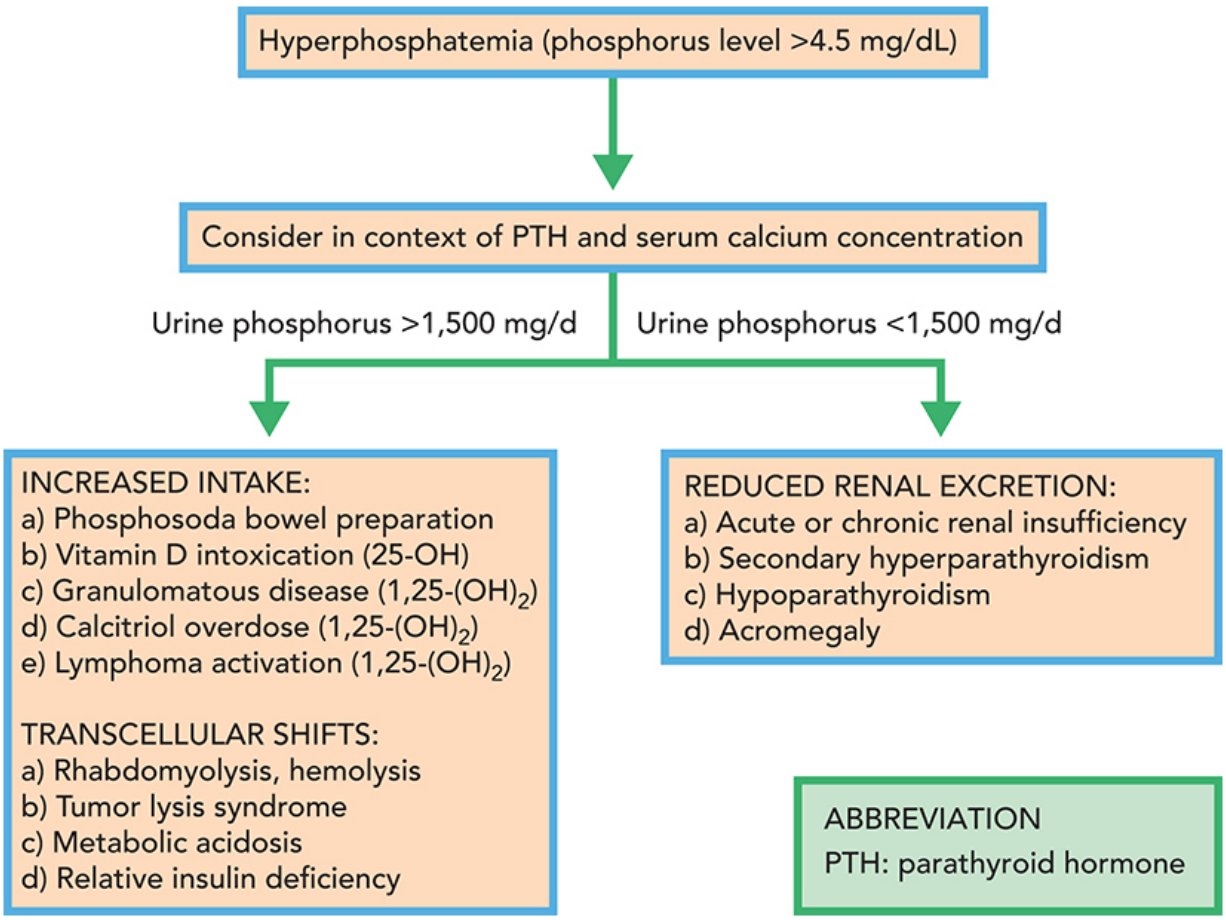
IBW, ideal body weight; IV, intravenous; PO, by mouth.

[a]Two IV preparations exist: use potassium phosphate if normal renal function and $[K^+]$ <4 mEq/L; use sodium phosphate if renal function is impaired or $[K^+]$ >4 mEq/L.

HYPERPHOSPHATEMIA

When evaluating hyperphosphatemia (Algorithm 26.10), the vitamin D level and PTH activity should be assessed. The kidneys possess a remarkable ability to excrete phosphorus, but retention may result if there is acute or chronic renal damage. Chronic kidney disease often leads to secondary hyperparathyroidism, with increased phosphorus despite the elevated PTH and with variable calcium concentrations. When increased intake or transcellular shifts are responsible for hyperphosphatemia, the urinary excretion is often quite high in an attempt to correct the imbalance.

ALGORITHM 26.10 Evaluation of Hyperphosphatemia



Symptoms of hyperphosphatemia primarily relate to the concomitant hypocalcemia that results. Metastatic calcification of soft tissue, vasculature, cornea, kidney, and joints can occur. Calciphylaxis is characterized by ischemia and necrosis involving the small blood vessels of skin resulting from calcium and phosphorus deposition, seen primarily, though not exclusively, in patients with chronic kidney disease.

ETIOLOGIES OF SPECIAL IMPORTANCE IN THE CRITICALLY ILL PATIENT

Transcellular Shifts

Since the majority of phosphorus is sequestered intracellularly, any process that leads to widespread cell destruction (eg, rhabdomyolysis, hemolysis, tumor lysis syndrome) can lead to significant hyperphosphatemia. The calcium concentration is often decreased as

it complexes with the circulating phosphorus. Metabolic acidosis, especially lactic acidosis and DKA (with its concomitant relative insulin deficiency), can also result in phosphorus shifting out of cells.

Phosphate-Rich Bowel Preparations

Hyperphosphatemia can occur from the use of bowel preparatory oral sodium phosphate formulations or phosphate-containing enemas. Cases of acute kidney injury via acute phosphate nephropathy have been reported following use of these laxatives. Volume depletion and underlying renal insufficiency are risk factors that may predispose toward acute kidney injury.

TREATMENT

Treatment of hyperphosphatemia is outlined in Table 26.6. Saline diuresis may help in excreting some of the excess phosphorus in the acute overload state. Acetazolamide is particularly effective at encouraging phosphorus elimination. If these conservative measures are unsuccessful and the underlying cause is not rapidly reversible, dialysis may become necessary for very severe hyperphosphatemia. For cases where chronic kidney disease is the cause, dietary restriction combined with oral phosphate binders is recommended.

TABLE 26.6 Treatment of Hyperphosphatemia

General guidelines of therapy:
1. Correct underlying cause (if normal renal function and phosphate handling are achieved, hyperphosphatemia will usually correct within 12 h).
2. Consider forced saline resuscitation with addition of acetazolamide (15 mg/kg q4h).
3. When severe, especially when renal insufficiency is not rapidly reversible, consider hemodialysis or continuous renal replacement therapy.
4. When chronic, use phosphate binders (noncalcium based if concomitant hypercalcemia) and dietary restriction.

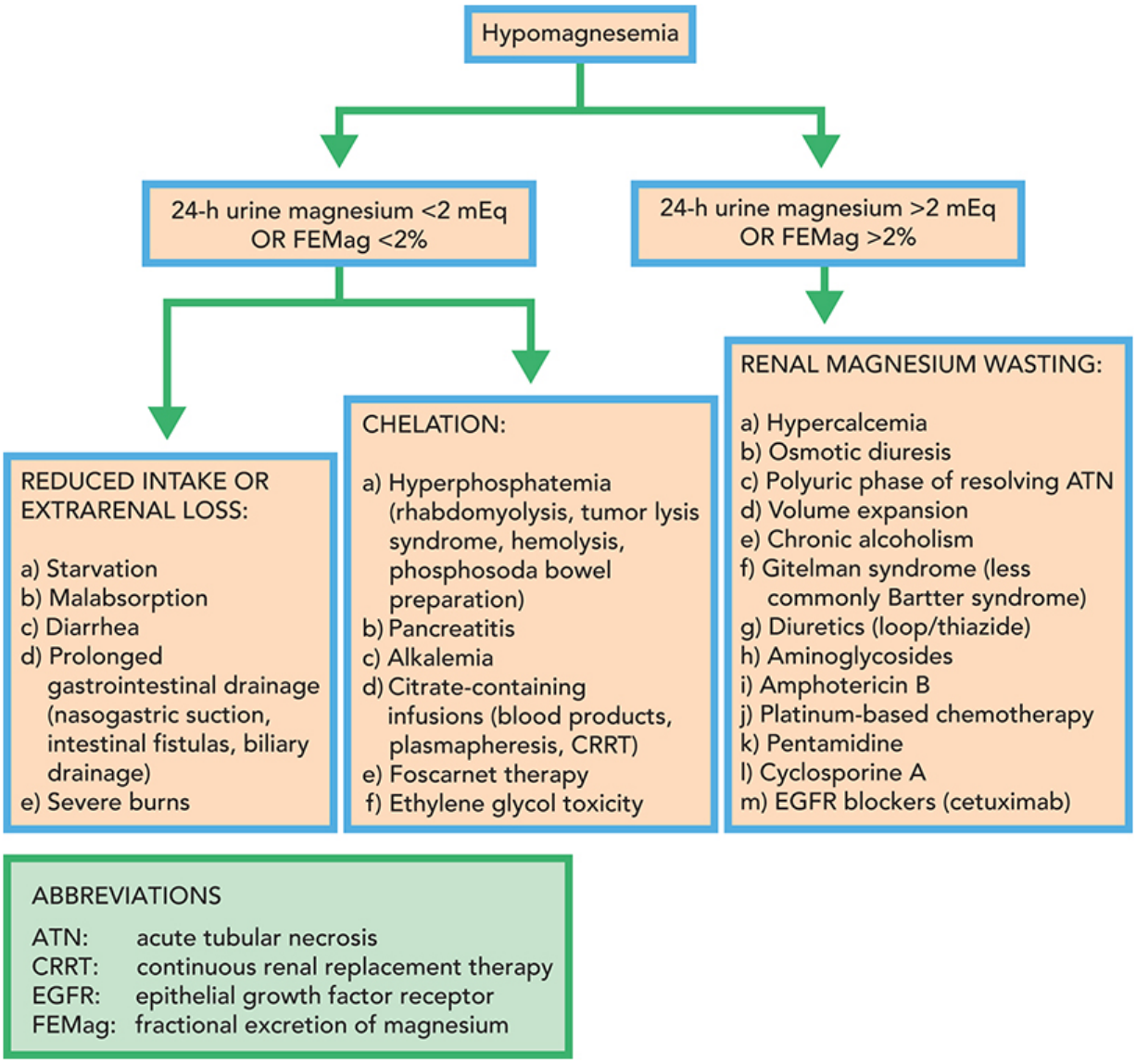
Disorders of Magnesium Concentration

Approximately 60% of body magnesium is in bone, and most of the remainder is within cells. Only 1% of the total magnesium is in the ECF. Mg^{2+} is not exchanged easily across the cell membrane, and therefore, there is little buffering of fluctuations in the serum Mg^{2+} concentration. Furthermore, the $[Mg^{2+}]$ is a poor predictor of intracellular and total body stores. Some of the regulators of calcium, such as PTH and calcitriol, also have an overlapping role in regulating magnesium levels.

HYPOMAGNESEMIA

Hypomagnesemia occurs commonly in the ICU. As an important participant in most processes involving calcium flux and a cofactor in reactions consuming ATP, Mg^{2+} is critical for many biologic processes. Algorithm 26.11 describes the primary etiologies of hypomagnesemia. Urinary losses in renal wasting have a fractional excretion of magnesium greater than 2%. This is calculated as (urine Mg^{2+} × serum creatinine)/(0.7 × serum Mg^{2+} × urine creatinine). Also, there may be gastrointestinal losses, reduced intake, or chelation (similar process as in hypocalcemia).

ALGORITHM 26.11 **Evaluation of Hypomagnesemia**



Symptoms of hypomagnesemia generally do not occur until the [Mg^{2+}] is less than 1 mEq/L. Lethargy, confusion, ataxia, nystagmus, tremor, fasciculations, tetany, and seizures may occur. Atrial and ventricular arrhythmias may be seen, particularly in patients on digoxin. The ECG may show prolonged PR and QT intervals with widened QRS complexes and U waves. Torsade de pointes is the classically associated arrhythmia with hypomagnesemia. There may be concurrent hypokalemia and hypocalcemia (particularly in patients with chronic alcohol consumption) and may contribute to the overall clinical picture.

ETIOLOGIES OF SPECIAL IMPORTANCE IN THE CRITICALLY ILL PATIENT

Gastrointestinal Loss

Intestinal secretions have significant Mg^{2+} content, with more magnesium present in lower intestinal fluids. Fistulas, prolonged gastrointestinal drainage, or diarrhea can therefore lead to negative Mg^{2+} balance.

Renal Wasting

Chronic alcohol ingestion may lead to renal tubular dysfunction, resulting in inappropriate Mg^{2+} wasting, exacerbating the malnutrition that is often present. Numerous drugs have similarly been associated with urinary Mg^{2+} wasting. Prolonged dosing of aminoglycosides may cause renal tubular damage with characteristic Mg^{2+} wasting and polyuria. The development of hypomagnesemia may even be delayed until after completion of therapy, and the tubular transport defect can persist for months. Other common offenders are the platinum-based chemotherapies such as cisplatin and carboplatin. Cetuximab is an epithelial growth factor receptor (EGFR) antagonist used in a variety of malignancies and can cause severe hypomagnesemia by its effect on the distal convoluted tubule.

Chelation

Because Mg^{2+} is an ion with similar charge and size as Ca^{2+}, similar causes of hypocalcemia from chelation can also result in hypomagnesemia, although usually to a lesser degree. This phenomenon has been described, for instance, in cases of severe acute pancreatitis. Hypomagnesemia worsens the hypocalcemia in this setting through its inhibition of PTH release.

TREATMENT

Hypomagnesemia treatment is outlined in Table 26.7. The route of Mg^{2+} repletion depends on whether clinical manifestations from Mg^{2+} deficiency are present and not on the specific Mg^{2+} level. Asymptomatic hypomagnesemia without ECG abnormalities can be

treated orally, even if the deficiency is severe, unless malabsorption is present. Oral therapy avoids the abrupt increase in [Mg^{2+}] that occurs with IV repletion, which then increases renal excretion of part of the administered dose. The major side effect of enteral therapy is diarrhea. In scenarios with chronic urinary Mg^{2+} wasting, potassium-sparing diuretics like amiloride can be administered to reduce renal losses. Symptomatic hypomagnesemia should be treated parenterally initially to replenish intracellular stores. Deep tendon reflexes should be tested frequently during aggressive parenteral dosing, as hyporeflexia implies the development of hypermagnesemia. Reduced doses and more frequent monitoring must be used even in mild renal insufficiency.

TABLE 26.7 Treatment of Hypomagnesemia

1. If ECG changes or symptoms present, begin IV replacement (reduce doses in renal insufficiency):
   a. 1-2 g $MgSO_4$ (1 g $MgSO_4$ = 96 mg elemental Mg^{2+} = 8 mEq Mg^{2+}) IV over 15 min, followed by an infusion of 6 g $MgSO_4$ in 1 L IV fluid over 24 h
   b. Continuous infusion may be required for 3-7 d to replenish total body stores; follow [Mg^{2+}] q24h (more frequently if renal insufficiency present) and adjust infusion to maintain [Mg^{2+}] <2.5 mEq/L.
   c. Check deep tendon reflexes often to detect developing hypermagnesemia.
2. If asymptomatic and no ECG changes:
   a. For mild hypomagnesemia: 240 mg PO elemental[a] Mg^{2+} per day in divided doses
   b. For severe hypomagnesemia: up to 720 mg PO elemental[a] Mg^{2+} per day in divided doses
   c. If PO not possible or diarrhea present: 2-6 g IV $MgSO_4$ infused at 1 g/h or less
3. For chronic hypomagnesemia from renal wasting, consider high-dose amiloride.

ECG, electrocardiogram; IV, intravenous.

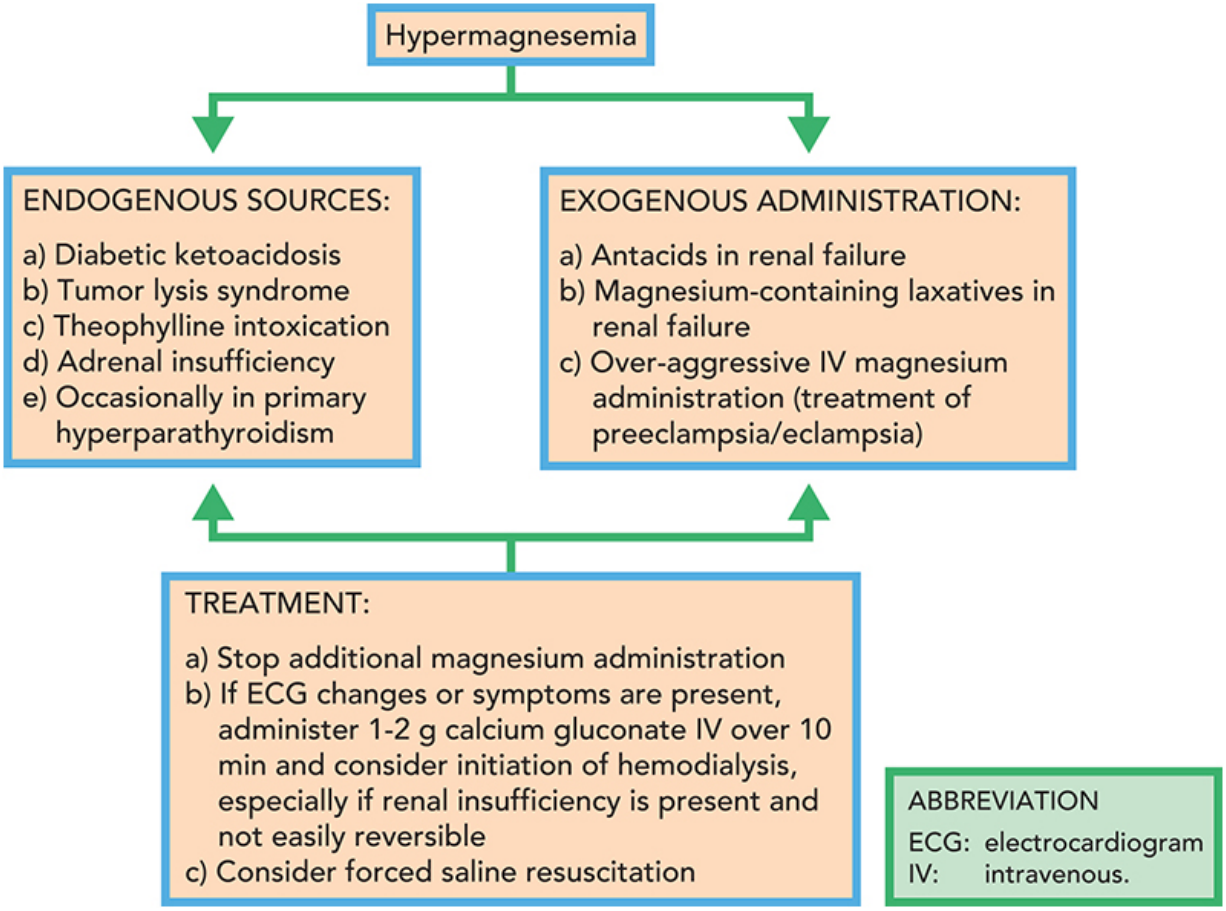
[a]Magnesium oxide = 0.6 mg elemental Mg^{2+} per mg.

HYPERMAGNESEMIA

The kidneys have a remarkable capacity to excrete excess magnesium and therefore it is uncommon to see hypermagnesemia unless concomitant renal insufficiency is present. Symptoms are typically seen only if the serum [Mg^{2+}] is greater than 4 mEq/L, and patients present with neuromuscular manifestations including hyporeflexia (usually the first sign of magnesium toxicity), weakness, and lethargy that can progress to somnolence and paralysis. With diaphragmatic involvement, this can lead to respiratory failure. Cardiac manifestations include hypotension, bradycardia, and cardiac arrest. The ECG may show prolonged PR, QRS, and QT intervals when the magnesium is 5 to 10 mEq/L. With more severe hypermagnesemia (>15 mEq/L), complete heart block or asystole may ensue.

The diagnostic differential is summarized in Algorithm 26.12. Treatment is focused on the cardiac manifestations, with administration of calcium gluconate to stabilize the myocardium. Exogenous magnesium should be discontinued and dialysis may be needed if renal insufficiency is present and not easily reversible (Algorithm 26.12).

ALGORITHM 26.12 Evaluation and Treatment of Hypermagnesemia


Hypermagnesemia
ENDOGENOUS SOURCES:
a) Diabetic ketoacidosis
b) Tumor lysis syndrome
c) Theophylline intoxication
d) Adrenal insufficiency
e) Occasionally in primary hyperparathyroidism
EXOGENOUS ADMINISTRATION:
a) Antacids in renal failure
b) Magnesium-containing laxatives in renal failure
c) Over-aggressive IV magnesium administration (treatment of preeclampsia/eclampsia)
TREATMENT:
a) Stop additional magnesium administration
b) If ECG changes or symptoms are present, administer 1-2 g calcium gluconate IV over 10 min and consider initiation of hemodialysis, especially if renal insufficiency is present and not easily reversible
c) Consider forced saline resuscitation
ABBREVIATION
ECG: electrocardiogram
IV: intravenous.

SUGGESTED READINGS

Adrogué H, Madias N. Aiding fluid prescription for the dysnatremias. *Intensive Care Med.* 1997;23:309-316.

The original paper first presenting the use of the Adrogué-Madias equation for planning initial therapy in the dysnatremias. The concepts underlying the equation and its derivation are presented. Several examples with a comparison to the prior approach are also given.

Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. *Am J Kidney Dis.* 1996;28:508-514.

The time course of the acute therapies for hyperkalemia is studied and compared. This is one of several papers confirming the relative ineffectiveness of bicarbonate in the acute treatment of hyperkalemia.

Amanzadeh J, Reilly RF. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nat Clin Pract Nephrol.* 2006;2:136-148.

SECTION V Acid-Base Disorders

27 Metabolic Acid-Base Disorders

Marco Thierry and Steven Cheng

Acid-base disorders are commonly encountered in critical care settings. A stepwise approach in evaluating these disorders helps delineate underlying causes, compensatory mechanisms, and the correct approach to management. This section will review the diagnosis and management of metabolic acidosis and alkalosis. Respiratory acidosis and alkalosis are discussed separately (see Chapter 26, Electrolyte Abnormalities).

The average individual generates a daily production of approximately 15,000 mmol of carbon dioxide (CO_2) and 50 to 100 mEq of hydrogen ions (H^+) from the catabolism of carbohydrates, fats, and proteins. An appropriate response to this acid load is essential because the range of extracellular H^+ concentration compatible with life (150-15 nmol/L and a respective pH of 6.8-7.8) is fairly narrow. Disorders of the acid-base system and the appropriate management are best understood by examining the equation for the bicarbonate-carbon dioxide buffer system:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO^-_3$$

The enzyme carbonic anhydrase catalyzes the reaction of water (H_2O) and carbon dioxide (CO_2) to form carbonic acid (H_2CO_3). Carbonic acid dissociates into bicarbonate HCO^-_3) and a hydrogen ion (H^+). The physiologic pH is thus balanced by respiratory processes, which adjust the partial pressure of CO_2 (P_{CO_2}), and metabolic processes, which modulate the generation and excretion of bicarbonate and hydrogen ions in the kidney.

When acid-base homeostasis is disturbed by a metabolic acidosis or alkalosis, respiratory compensation is required to attenuate the degree of change in pH. In metabolic acidosis, this compensation begins immediately, although the full degree of compensation (a decrease in P_{CO_2} of 1.2 mm Hg for each 1 mEq/L decrease in the serum bicarbonate) may not be completely attained for 12 to 24 hours. In metabolic alkalosis, the appropriate respiratory response is a 0.7-mm Hg increase in the P_{CO_2} for each 1 mEq/L increase in the serum bicarbonate (Table 27.1). However, the hypoventilation required for an increase in P_{CO_2} is often not possible for patients who are critically ill with underlying cardiac and pulmonary disorders.

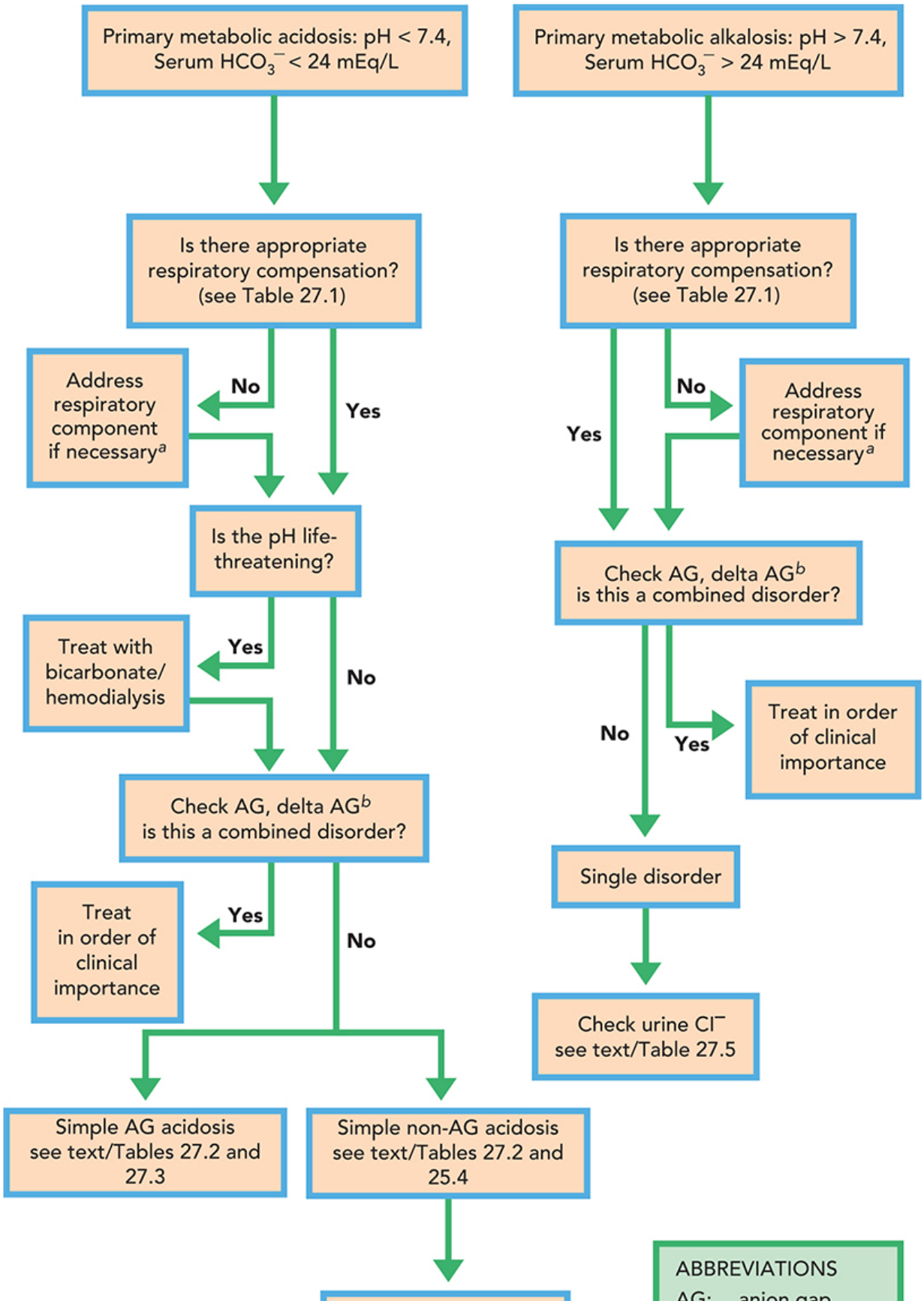
TABLE 27.1 Expected Pco_2 and Respiratory Compensation for Metabolic Acidosis and Alkalosis

Metabolic acidosis	Pco_2 is >10 mm Hg in a single disorder.
	Pco_2 is −1.2 mm Hg for every 1 mEq/L fall in HCO^-_3] (below 24 mEq/L).
Metabolic alkalosis	Pco_2 is <60 mm Hg in a single disorder.
	Pco_2 is +0.7 mm Hg for every 1 mEq/L rise in HCO^-_3] (above 24 mEq/L).

The clinical identification of metabolic acid-base disorders, the evaluation of respiratory compensation, and the detection of mixed disorders requires a careful systematic approach. The following steps represent one such approach (Algorithm 27.1):

1. Determine the underlying abnormality—metabolic acidosis and/or metabolic alkalosis.
2. Determine the contributing factors and concomitant disorders (anion gap [AG] acidosis ± non-AG acidosis ± metabolic alkalosis).
3. Evaluate the appropriateness of respiratory compensation.
4. Determine the likely cause of the disorder and whether urgent intervention is necessary.

ALGORITHM 27.1 Approach to Metabolic Acidosis and Alkalosis


Primary metabolic acidosis: pH < 7.4, Serum HCO_3^- < 24 mEq/L
Is there appropriate respiratory compensation? (see Table 27.1)
No
Address respiratory component if necessary[a]
Yes
Is the pH life-threatening?
Yes
Treat with bicarbonate/ hemodialysis
No
Check AG, delta AG[b] is this a combined disorder?
Yes
Treat in order of clinical importance
No
Simple AG acidosis see text/Tables 27.2 and 27.3
Simple non-AG acidosis see text/Tables 27.2 and 25.4
Primary metabolic alkalosis: pH > 7.4, Serum HCO_3^- > 24 mEq/L
Is there appropriate respiratory compensation? (see Table 27.1)
No
Address respiratory component if necessary[a]
Yes
Check AG, delta AG[b] is this a combined disorder?
Yes
Treat in order of clinical importance
No
Single disorder
Check urine Cl^- see text/Table 27.5
ABBREVIATIONS

[a]May require intubation and mechanical ventilation for patients with life-threatening acid-base disturbances unable to fully hyper- or hypoventilate appropriately.

[b]See text for details.

Metabolic Acidosis

Acidemia is the most common acute metabolic acid-base disturbance presenting in the critical care setting. The following are the four main mechanisms used in an attempt to maintain homeostasis in this setting:

1. Extracellular buffering primarily via HCO^-_3
2. Intracellular and bone buffering (buffers up to 55%-60% of the acid load)
3. Renal excretion of H^+ and regeneration of bicarbonate
4. Respiratory excretion of CO_2 by alveolar ventilation

Metabolic acidosis may present either as a single disturbance or as a more complex combined disorder due to various simultaneous processes with different effects on acid-base homeostasis. Double and triple metabolic disorders often reflect a metabolic alkalosis occurring with an AG acidosis (as seen during diabetic ketoacidosis and vomiting) and/or a non-AG acidosis. Inappropriate respiratory compensation in any of these situations may add the additional component of respiratory acidosis or alkalosis.

ANION GAP ACIDOSIS

The AG is a way of measuring “unmeasured” anions in the blood (as opposed to the “measured” chloride and bicarbonate anions typically identified in basic chemistry laboratory results). It can be calculated by the following equation:

$$\text{Anion Gap} = [\text{Serum Sodium } (Na^+) - (\text{Serum Chloride } [Cl^-] + \text{Serum } HCO^-_3)]$$

Normal values are between 8 and 12 mEq/L.

An AG greater than this simply suggests that the patient has been exposed to an “unmeasured” anion, which increases the AG. For example, the accumulation of lactate, beta hydroxybutyrate, and acetoacetate—all of which are unmeasured anions—increases the AG. Thus, common causes of an AG metabolic acidosis include lactic acidosis, toxic ingestions, ketoacidosis, rhabdomyolysis, and renal failure (Tables 27.2 and 27.3).

TABLE 27.2 Causes of Anion Gap and Nonanion Gap Metabolic Acidosis

	Mechanism
Increased Anion Gap Acidosis[a]	**Increased acid production or administration** Lactic acidosis: lactate, D-lactate Ketoacidosis Massive rhabdomyolysis Intoxications: Methanol/formaldehyde → formate Ethylene glycol → glycolate, oxalate Toluene → hippurate Salicylates Paraldehyde → organic anions L-5 oxoprolinuria **Decreased acid excretion (positive UAG)** Chronic renal failure
Normal Anion Gap Acidosis	**Increased bicarbonate loss or loss of bicarbonate precursors** GI losses (negative UAG) Diarrhea Pancreatic, biliary, intestinal fistulas Ostomy Cholestyramine Sevelamer Renal losses Carbonic anhydrase inhibitors Type 2 (proximal) RTA Treatment phase of ketoacidosis **Decreased acid excretion (positive UAG)** Acute renal failure Chronic renal failure Type 1 (distal) RTA Hypoaldosteronism (type 4 RTA) **Increased acid production or administration** Ammonium chloride ingestion Hyperalimentation fluids/saline infusion

GI, gastrointestinal; RTA, renal tubular acidosis; UAG, urine anion gap.
[a]See Table 27.3 for further discussion.

TABLE 27.3 Causes and Treatment of Anion Gap Metabolic Acidosis

Condition	Cause and Symptoms	Treatment	Comments

Condition	Cause and Symptoms	Treatment	Comments
Lactic acidosis Pyruvate ↕ Lactate	*Increased lactate production* 1. Increased pyruvate production: enzymatic defects in glycogenolysis or gluconeogenesis 2. Decreased pyruvate utilization: enzymatic defects in pyruvate dehydrogenase or carboxylase 3. Increased conversion of pyruvate to lactate: Increased metabolic rate Grand mal seizure Severe exercise Hypothermic shivering Shock/cardiac arrest/acute pulmonary edema Severe hypoxemia CO poisoning Cyanide intoxication *Decreased lactate utilization* Hypoperfusion Alcoholism Liver disease	Correction of the underlying disorder and reversal of circulatory failure is the primary therapy Sodium bicarbonate is controversial; consider if pH <7.1 or loss of buffering capacity (bicarbonate <5 mEq/L). Hemodialysis may be indicated in resistant cases. *Alternative therapies* (have not been demonstrated safe and effective in randomized controlled human studies) THAM (tromethamine)—inert amino alcohol that buffers acids without generating CO_2. Renally excreted and may produce hyperkalemia, hypoglycemia, and respiratory depression in anuric/oliguric patients Carbicarb—equimolar mixture of sodium carbonate and sodium bicarbonate. Diminished risk of hypercapnia and intracellular acidosis compared with sodium bicarbonate Dichloroacetate—activates pyruvate dehydrogenase, and increases oxidation of pyruvate, thus decreasing its conversion to lactate	*Caution with bicarbonate therapy* Volume overload Postrecovery metabolic alkalosis Hypernatremia Increased CO_2 production and possible retention in setting of circulatory failure with worsening of mixed venous P_{CO_2} Intracellular acidosis Reduction in ionized calcium and worsening of cardiac contractility
Propylene glycol toxicity	Converts to pyruvate and lactate Vehicle for lorazepam, etomidate, phenytoin and nitroglycerin, and other agents, and continuous infusion may result in lactate accumulation and increased osmolar gap.	Discontinue infusion	

Condition	Cause and Symptoms	Treatment	Comments
Ketoacidosis	In the setting of insulin deficiency Symptoms include vomiting, abdominal pain, severe volume depletion/dehydration.	Insulin and fluids—acidosis will improve with insulin-induced metabolism of ketoacids and regeneration of serum HCO_3.	
Salicylate toxicity	Toxicity when plasma level >40-50 mg/dL (therapeutic, 20-35 mg/dL) Mixed metabolic acidosis and respiratory alkalosis Increased ketoacid and lactate production Diagnosis—plasma salicylate level	Reduce salicylate levels to avoid neurotoxicity Alkalinization of plasma to a pH >7.45-7.5 converts salicylate to ionized form that lowers CNS levels Alkalinization of urine decreases renal tubular reabsorption of ionized salicylate. Consider hemodialysis for plasma concentration >80 mg/dL	If respiratory alkalosis is the primary disturbance, then further alkalinization is not necessary.
Methanol ↕ Formaldehyde ↕ Formic acid	Minimal lethal dose is 50-100 mL. Symptoms include weakness, headache, blurred vision, and blindness. Diagnosis—plasma methanol assay	The treatment for both methanol and ethylene glycol is identical. Prompt treatment is necessary and includes oral charcoal and sodium bicarbonate.	Simultaneous use of both ethanol and fomepizole is not recommended as fomepizole increases the half-life of ethanol.
Ethylene glycol ↓ Glycolic and oxalic acid	Component of antifreeze and solvents Symptoms include neurologic and cardiopulmonary abnormalities, flank pain, and renal failure. Envelope- and needle-shaped oxalate crystals may be visible in the urine. Diagnosis—plasma ethylene glycol assay	Administration of ethanol or fomepizole competes with or inactivates metabolism, respectively, of parent compound and prevents formation of toxic metabolites. Administration of folic acid, thiamine, and pyridoxine. Hemodialysis for removal of toxic metabolites and parent compound	

Condition	Cause and Symptoms	Treatment	Comments
L-5-Oxoproline toxicity	High anion gap acidosis in children secondary to congenital glutathione synthetase deficiency. Acquired oxoprolinuria associated with acetaminophen and other medications Renal dysfunction and sepsis predispose Diagnosis—negative toxicity screening and high plasma and urine levels of 5-oxoproline/urine organic acid screen	Treatment primarily includes cessation of the offending agent. *N*-Acetylcysteine may be beneficial; restoration of glutathione stores reduces L-5-oxoproline levels.	
D-Lactic acidosis (from bacterial overgrowth in the colon)	Associated with short gut syndrome and overproduction of D-lactate Symptoms: episodic anion gap acidosis (usually occurring after high-carbohydrate meals) and neurologic abnormalities including cerebellar ataxia, confusion, and slurred speech Diagnosis—enzymatic assay for D-lactate	Treatment includes sodium bicarbonate administration and antimicrobial agents.	

CNS, central nervous system; THAM, *tris*-hydroxymethyl aminomethane.

Of note, the normal range for the AG reflects the presence of physiologic unmeasured anions, such as albumin, in nonpathologic states. However, conditions that alter the concentrations of these unmeasured anions also alter the AG. For example, a 1 g/dL decrease in the serum albumin would be expected to decrease the AG by 2.5 to 3 mEq/L. It is important to adjust the AG for these changes in order to properly detect an AG acidosis that may be present despite a calculated AG that appears within the normal range of 8 to 12 mEq/L. The serum osmolal gap may also be of value when a toxic ingestion (ethanol, methanol, and ethylene glycol) is a suspected cause of an AG acidosis (Table 27.3). An increased osmolal gap is an otherwise nonspecific finding and may be seen in

other forms of AG acidosis. The normal osmolal gap is approximately 10 mOsm/kg.

$$\text{Osmolal gap} = \text{Measured serum osmolality} - \text{Calculated serum osmolality}$$

$$\text{Calculated serum osmolality} = 2[Na^+] + [\text{BUN}]/2.8 + [\text{glucose}]/18$$

NONANION GAP ACIDOSIS

Non-AG acidosis occurs in the setting of bicarbonate loss, but without the presence of an additional, pathologic anion. In a non-AG acidosis, $[Cl^-]$ is increased to maintain electroneutrality, and the calculated AG remains normal. The differential of non-AG acidosis includes gastrointestinal bicarbonate losses versus a renal etiology (Table 27.2).

In the setting of a non-AG acidosis, the appropriate renal response would be to increase ammonium excretion, as NH_4Cl. Therefore, urine ammonium levels can be used to evaluate whether the kidneys are responding appropriately to an acidosis (suggesting a nonrenal cause) or inappropriately (suggesting a renal cause). When direct measurements of urine ammonium are unavailable, the urine anion gap (UAG) can be used as a surrogate. The UAG can be calculated as follows:

An increase in urinary ammonium excretion would increase urine [Cl] as well, thus causing the UAG to become negative by as much as −20 to −50 mEq/L. In conditions with impaired renal acid excretion, such as chronic kidney disease (CKD) and distal renal tubular acidosis (RTA), the UAG may remain positive or become only slightly negative. While the UAG has been frequently used in clinical practice, its utility is limited in the setting of hypovolemia, oliguria, low urine $[Na^+]$, or in AG acidosis, and direct measurement of urine ammonium is preferable when available.

RENAL TUBULAR ACIDOSIS

These disorders are characterized by a hyperchloremic metabolic acidosis resulting from diminished capacity of the kidney to accommodate the acid load. A diagnosis of RTA cannot be made in the setting of acute renal failure or with moderate-to-severe CKD. Although RTA is generally a chronic condition and rarely causes acute critical illness, the identification of an RTA in the critical care setting is important. It may point clinicians toward underlying conditions that are associated with various forms of RTA. Distal (type 1) RTA is associated with drugs like amphotericin and autoimmune conditions such as lupus and Sjögren syndrome. Proximal (type 2) RTA is associated with multiple myeloma and may manifest with profound wasting of solutes that are typically reabsorbed in the proximal tubule such as glucose and phosphorus. Type 4 RTA, which is due to

hyporeninemic hypoaldosteronism, is a commonly seen manifestation of diabetes and is closely linked to hyperkalemia. A detailed discussion of this topic is beyond the intent of this manual (Table 27.4).

TABLE 27.4 Renal Tubular Acidosis (RTA)

	Distal (Type 1) RTA	Proximal (Type 2) RTA	Hyporeninemic Hypoaldosteronism (Type 4) RTA
Causes	Idiopathic, familial, Sjögren syndrome, hypercalciuria, rheumatoid arthritis, sickle cell anemia, SLE, amphotericin	Idiopathic, multiple myeloma, carbonic anhydrase inhibitors, heavy metals (lead, mercury), amyloidosis, hypocalcemia, and vitamin D deficiency	Diabetes, ACE inhibitors, tubulointerstitial nephritis, NSAIDs, heparin, adrenal insufficiency, obstructive uropathy, K^+-sparing diuretics
Defect	Impaired distal tubular H^+ excretion (distal acidification)	Impaired proximal tubular bicarbonate absorption with/without associated glycosuria, aminoaciduria, and phosphaturia	Aldosterone deficiency or resistance
Plasma HCO^-_3	Variable; usually more severe acidosis with level <10 mEq/L	Less severe acidosis than distal RTA; usually 12-20 mEq/L	Usually >15 mEq/L
Urine pH during acidemia[a]	>5.3	Variable; >5.3 if serum HCO^-_3 is above the reabsorptive threshold. The excessive bicarbonate "spills out" into the urine causing a high urine pH. <5.3 if serum HCO^-_3 is below threshold.	Usually <5.3
Plasma K^+	Usually low; usually corrects with alkali therapy	Low; usually worsened by bicarbonaturia seen with alkali therapy	High
UAG	Positive	Variable; not helpful	Positive
Associated conditions	Renal stones/nephrocalcinosis	Rickets/osteomalacia/Fanconi syndrome	None

	Distal (Type 1) RTA	Proximal (Type 2) RTA	Hyporeninemic Hypoaldosteronism (Type 4) RTA
Treatment	Alkali therapy: sodium citrate/potassium citrate/sodium bicarbonate	Alkali therapy: higher doses are needed because of bicarbonaturia. Thiazide diuretics may be tried in resistant cases.	Treat the cause of hypoaldosteronism/low potassium diet/loop diuretics

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus; UAG, urine anion gap.

[a]In metabolic acidosis with intact renal acid excretion, urine pH should be <5 to 5.3.

TREATMENT

In patients with metabolic acidosis, the first goal of therapy is to identify and correct the underlying cause. The various causes and mechanisms of metabolic acidosis are listed in Table 27.2. Reversal of these underlying processes is of great importance and can often be sufficient to improve the acidemia. A common example of this can be illustrated in patients with diabetic ketoacidosis, who have prompt improvement with the administration of insulin and fluids.

However, not all causes can be rapidly reversed, and patients who are exposed to severe and/or prolonged acidemia are at risk for a variety of complications, including prolonged compensatory hyperventilation, deranged enzymatic activity, depressed cardiac contractility, reduced responsiveness to vasopressors, and arteriolar vasodilation. Because these sequelae may result in severe respiratory, metabolic, and cardiovascular consequences, attenuation of the acidemia should be considered when underlying causes cannot be immediately reversed.

The role of alkali therapy in attenuating acute metabolic acidosis depends on various factors, including underlying etiology, chronicity, severity, and reversibility. Sodium bicarbonate therapy is controversial since bicarbonate therapy itself can result in volume expansion, increased P_{CO_2} generation, hypernatremia, and hypocalcemia, all of which may contribute toward worsening cardiovascular depression. However, expert opinion favors administrating bicarbonate in life-threatening acidemia, with a pH less than 7.1 to 7.2. This is based on limited data suggesting a mortality benefit at this degree of acidemia (sodium bicarbonate therapy for patients with severe metabolic academia in the intensive care unit [BICAR-ICU]: a multicenter, open-label, randomized controlled, phase 3 trial). The total amount of bicarbonate required to correct a metabolic acidosis can be roughly approximated by calculating a patient's bicarbonate deficit.

$$\text{Bicarbonate deficit (mEq)} = \text{Apparent volume of distribution} \times \text{target change in } [HCO^-_3]$$

$$\text{Apparent volume of distribution} = \text{Total body weight (kg)} \times [0.4 + (2.4/HCO^{-}_{3}])]$$

For example, to increase the serum bicarbonate to 12 mEq/L in a 60-kg patient with a serum bicarbonate level of 5 mEq/L:

$$\text{Apparent volume of distribution} = 60\ \text{kg} \times [0.4 + 2.4/5] = 53\ \text{L}$$

$$\text{Target change in } HCO^{-}_{3}] = 12\ \text{mEq/L} - 5\ \text{mEq/L} = 7\ \text{mEq/L}$$

$$53\ \text{L} \times 7\ \text{mEq/L} = 371\ \text{mEq}$$

This amount of bicarbonate can be administered over a minimum of 4 to 8 hours with frequent monitoring of both HCO^{-}_{3}] and pH.

There are other agents that buffer H+ protons without increasing CO_2, including *tris*-hydroxymethyl aminomethane (THAM) and dichloroacetate (via increased oxidation of pyruvate). While THAM has been available for a number of years, there is little outcome data on mortality benefit, and no clinical trials regarding its use in lactic acidosis have been done. It should be used cautiously in patients with impaired renal function, as it is excreted by the kidneys, and accumulation can lead to toxicity (primarily hyperkalemia). Continuous or intermittent hemodialysis may also be used to correct severe, refractory acidosis, particularly in patients with concomitant renal injury or in patients who cannot accommodate the volume associated with administration of intravenous bicarbonate-containing fluids. Most dialysate solutions have a bicarbonate concentration of 35 to 38 mEq/L.

Patients with chronic metabolic acidosis, often resulting from CKD or renal tubular dysfunction, are managed very differently from those with acute metabolic acidosis. While the degree of acidemia is generally less severe in patients with chronic acidosis, the persistently acidemic milieu is associated with bone demineralization, protein catabolism, and progression of CKD in untreated patients. Administration of oral alkali therapy, typically oral sodium bicarbonate, is usually sufficient to prevent these long-term complications. In small studies, correction of chronic metabolic acidosis has resulted in preservation of glomerular filtration rate (GFR), reduction in proteinuria, and a modest mortality benefit.

Metabolic Alkalosis

Most cases of metabolic alkalosis encountered in the intensive care unit are induced by diuretics or the loss of gastric secretions due to vomiting or nasogastric suctioning. Other causes include bicarbonate administration, the posthypercapnic state, and citrate associated with centrifugal plasma exchange,

massive transfusion, or fresh frozen plasma administration. The condition is often aggravated by renal insufficiency, which delays bicarbonate excretion. Because alkalemia promotes the release of protons bound to albumin, the negative charge of albumin can increase in metabolic alkalosis, resulting in a slight AG. Metabolic alkalosis can also be combined with other disorders, such as gap and nongap acidosis, in mixed acid-base disorders. Metabolic alkalosis can be broadly categorized into a chloride-responsive or chloride-resistant process (Table 27.5).

TABLE 27.5 Chloride-Responsive and Chloride-Resistant Metabolic Alkalosis

Chloride Responsive (Urinary Cl^- ≤25 mEq/L)	Chloride Resistant (Urinary Cl^- >25 mEq/L)
Loss of gastric H^+—vomiting or gastric suction Prior loop/thiazide diuretic use Chloride-losing diarrhea: villous adenoma/some cases of factitious diarrhea due to laxative abuse Cystic fibrosis (high sweat Cl^-) Posthypercapnia	Mineralocorticoid excess: primary hyperaldosteronism, Cushing or Liddle syndrome, exogenous steroid use, licorice ingestion Active loop/thiazide diuretic use Bartter or Gitelman syndrome Alkali load: exogenous bicarbonate infusion, citrate-containing blood products, antacids (milk-alkali syndrome). Severe hypokalemia
Treatment includes administration of 0.9% or 0.45% NaCl and repletion of potassium stores.	**Treatment is disease-specific and includes repletion of potassium stores.**

COMMON CAUSES OF METABOLIC ALKALOSIS

Gastric Secretion Loss

Gastric secretions are lost through removal of gastric contents by tube drainage or due to vomiting. Normally, hydrogen ions released into the stomach reach the duodenum, where they stimulate pancreatic bicarbonate secretion into the gastrointestinal tract, maintaining acid-base balance. When gastric contents are lost, bicarbonate is not secreted, resulting in increased plasma bicarbonate and metabolic alkalosis. Self-induced vomiting is often denied by patients with eating or factitious disorders, and a low urine chloride supports the diagnosis.

Contraction Alkalosis

Contraction alkalosis occurs in the setting of excessive loss of chloride-rich, bicarbonate-free fluid. This is most commonly seen with the use of loop or thiazide diuretics, but can also occur with gastric losses or with cystic fibrosis (high sweat [Cl^-]). As a result of “contraction” of the extracellular volume, there is

a relative increase in the bicarbonate concentration. Despite the relative intravascular volume depletion, there is an obligate urinary loss of sodium with bicarbonate in this setting. Therefore, urine chloride concentration is usually a better predictor of the volume status in this form of metabolic alkalosis than urine sodium.

Posthypercapnic Alkalosis

Chronic respiratory acidosis is associated with an appropriate compensatory increase in the serum bicarbonate concentration. Sudden normalization of a chronically elevated P_{CO_2} via mechanical ventilation can result in an acute, potentially lethal increase in the pH. Therefore, the P_{CO_2} should not be decreased rapidly in the setting of a well-compensated chronic respiratory acidosis.

Refeeding Syndrome

Patients fed a high-carbohydrate diet after a prolonged fast can acutely develop metabolic alkalosis. Intracellular hydrogen ion shift is the proposed mechanism. Refeeding may also be independently associated with hypophosphatemia.

Severe Hypokalemia

Severe hypokalemia via multiple renal mechanisms causes hydrogen ion secretion and bicarbonate reabsorption. The ensuing metabolic alkalosis is refractory to treatment until potassium stores are replaced.

Milk-Alkali Syndrome

Milk-alkali syndrome results from a chronic high calcium intake (usually in the form of calcium-containing antacids) and is usually associated with renal insufficiency.

TREATMENT

Intravenous sodium chloride fluid administration will reverse chloride-responsive metabolic alkalosis (Table 27.5). Response to treatment can be monitored via urine pH and urine chloride concentration. Concomitant hypokalemia may also play a critical role in the maintenance of metabolic alkalosis, as it increases tubular secretion of H^+ and reabsorption of bicarbonate. Patients with hypokalemia and alkalosis may have a profound total body potassium deficit, and treatment of this will be necessary in the correction of metabolic alkalosis. If the patient is able to take medication by mouth, oral supplementation is preferred with potassium chloride 40 mEq every 4 to 6 hours. Alternatively, if the patient is unable to take medication enterally, intravenous infusion of potassium chloride at a rate of 10 mEq/h with close monitoring of serum potassium may be initiated.

Acetazolamide can be considered in cases of worsening metabolic alkalosis associated with volume overload complicated by the need for continued attempts at diuresis (nonchloride responsive). Acetazolamide inhibits carbonic anhydrase, the enzyme that catalyzes the conversion of CO_2 and water into carbonic acid, causing renal excretion of hydrogen ions and retention of bicarbonate. Decreased bicarbonate excretion from carbonic anhydrase inhibition causes a metabolic acidosis to counter the alkalosis. Acetazolamide has minimal diuretic effects as a single agent, but can have additive effects when combined with loop and/or thiazide diuretics if the serum bicarbonate concentration is elevated.

In cases of severe, refractory alkalosis (usually associated with bicarbonate administration in the setting of renal failure), hydrochloric acid infusion through a central line is rarely needed, but can be used. Other alternatives include the use of intermittent hemodialysis with the bicarbonate bath decreased to the lowest allowable value (limited bicarbonate gradient available with most systems) or a continuous hemofiltration modality using primarily a nonbicarbonate, noncitrate replacement fluid.

Mixed Acid-Base Disorders

The delta AG is a useful ratio in determining the presence of other metabolic disturbances superimposed on a known AG acidosis. It is calculated as follows:

$$\text{Delta Anion Gap } (\Delta/\Delta): \quad \frac{\Delta^*\text{AG (from normal, which is approximately 10)}}{\Delta^*\text{HCO}_3 \text{ (from normal, which is approximately 25 mEq/L)}}$$

$$\Delta^*\text{AG} = \text{Patient calculated AG} - \text{Normal AG}$$

$$\Delta^*\text{HCO}_3 = \text{Serum HCO}_3 - \text{Normal HCO}_3$$

The delta gap is a ratio based on the principle that the change in AG should roughly approximate the change in serum bicarbonate in a simple AG acidosis.

A ratio of less than 1 occurs if the drop in serum bicarbonate is greater than the change in the AG. This indicates a disproportionate fall in serum bicarbonate due to a concomitant non-AG acidosis, which, as expected, would not have a large change in AG. A ratio greater than 1 would indicate that there was a larger change in the AG without the expected drop in serum bicarbonate, suggesting there is an underlying metabolic alkalosis.

Elucidation of double or triple acid-base disturbances requires assessment of multiple metabolic parameters. Because complex acid-base disorders may at first manifest with several normal-appearing lab values, a methodical evaluation of all data (including the calculation of AG and delta gap) should be done routinely. The

following patterns are often suggestive of a combined acid-base disturbance despite a “normal” pH:

Normal pH + ↓ P_{CO_2} + ↓ H_{CO_3}: respiratory alkalosis plus metabolic acidosis

Normal pH + ↑ P_{CO_2} + ↑ H_{CO_3}: respiratory acidosis plus metabolic alkalosis

Normal pH + normal P_{CO_2} + normal H_{CO_3} + ↑ AG: metabolic acidosis and alkalosis

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28 Respiratory Acid-Base Disorders

Michael Paul Wassermann

Respiratory acid-base disorders are commonly encountered in the critical care setting and can occur independently or coexist with metabolic acid-base disorders (metabolic disorders are discussed separately in Chapter 27, Metabolic Acid-Base Disorders). Evaluation of respiratory acid-base disorders can be relatively straightforward in patients with an isolated, acute primary respiratory acidemia/alkalemia or more complicated when superimposed metabolic acid-base disorders are present. When discussing acid-base disorders, whether respiratory or metabolic, it should be noted that the term “acidemia” refers to a blood pH less than 7.35, whereas “acidosis” is the process leading to the state of “acidemia.” Similarly, “alkalemia” refers to a blood pH greater than 7.45 and “alkalosis” is the process leading to a state of alkalemia. In this sense, a patient can be experiencing an alkalosis or acidosis without being acidemic or alkalemic if their pH is between 7.35 and 7.45.

Respiratory acid-base disorders are defined by altered plasma carbon dioxide levels as measured on arterial blood gas (ABG) analysis by the partial pressure of carbon dioxide ($Paco_2$). Respiratory acidemia is characterized by an elevated $Paco_2$ and decreased pH, whereas respiratory alkalemia is defined by a decreased $Paco_2$ and elevated pH. The $Paco_2$ in healthy adults is 35 to 45 mm Hg and the normal pH is 7.35 to 7.45. For calculation purposes, it is reasonable to use 40 mm Hg as the baseline normal $Paco_2$ level and 7.4 as the baseline normal pH (Table 28.1). In respiratory acid-base disorders, the kidneys compensate for changes in the $Paco_2$ by adjusting excretion of bicarbonate (HCO_3^-) accordingly. In healthy adults, the serum HCO_3^- is generally 22 to 26 mEq/L. Thus, it is reasonable to use a level of 24 mEq/L for

calculation purposes (Table 28.2). Acute respiratory acid-base disorders result in small changes in the bicarbonate concentration, and cellular buffering predominates. Renal compensation occurs slowly, taking at least 24 to 72 hours to fully develop, and results in larger changes in serum HCO_3^-. Compensatory changes in serum HCO_3^- result in the pH shifting back toward, but never reaching, normal. Mixed acid-base disorders do not include the renal bicarbonate compensation that occurs for acute and chronic respiratory acid-base disorders and are present any time the pH is normal with an abnormal $Paco_2$. Algorithm 28.1 provides a step-wise approach to analyzing a respiratory acid-base disorder.

ALGORITHM 28.1 **Approach to Respiratory Acid-Base Disorders**

Step 1—Review ABG and basic metabolic panel and check for internal validity. Obtain an ABG and ensure the serum bicarbonate [HCO_3^-] is accurate using the Henderson-Hasselbalch equation (Table 28.1).

$$[H^+] = 24\,[HCO_3^-]/Paco_2$$

The [HCO_3^-] reported on the ABG and basic metabolic panel should also agree within 2 mmol/L.

Step 2—Determine the primary acid-base disturbance (metabolic acid-base disorders are discussed in Chapter 27). A primary respiratory acid-base disorder is present if the $Paco_2$ is altered and the change in pH is in the opposite direction.

- Respiratory acidemia = $Paco_2$ >45 mm Hg and pH <7.35
- Respiratory alkalemia = $Paco_2$ <35 mm Hg and pH >7.45

Step 3—Determine if the respiratory acid-base disorder is uncompensated (acute) or compensated (chronic). *The pH will approach, but never reach normal* (see Table 28.2).

- A serum HCO_3^- or pH that deviates significantly from expected suggests a superimposed metabolic acid-base disorder.

Step 4—Determine if a mixed respiratory and metabolic acid-base disorder is present—if the change in pH is *more* than expected for the given $Paco_2$ (see Table 28.2).

- A combined metabolic *and* respiratory acidemia is present if the *decrease* in pH is greater than expected based on the $Paco_2$.

$$\Delta pH = \left(\frac{\Delta Paco_2}{10}\right) \cdot 0.08$$

  - Example—pH 7.1 with a $Paco_2$ of 60 mm Hg. $\Delta pH = \left(\frac{20}{10}\right) \cdot 0.08 = 0.16$.
    7.4 – 0.16 = expected pH of 7.24. Thus a superimposed metabolic acidosis exists.

- A combined metabolic *and* respiratory alkalemia is present if the *increase* in pH is greater than expected.
  - Example—pH 7.55 with a $Paco_2$ of 30 mm Hg. $\Delta pH = \left(\frac{10}{10}\right) \cdot 0.08 = 0.08$.
    7.4 + 0.08 = expected pH of 7.48. Thus a superimposed metabolic alkalosis exists.

- A normal pH in the setting of an abnormal $Paco_2$ indicates a mixed acid-base disorder.

  - Example—pH 7.38 with a $Paco_2$ of 60 mm Hg indicates a respiratory acidosis with a metabolic alkalosis.
  - Example—pH 7.42 with a $Paco_2$ of 30 mm Hg indicates a respiratory alkalosis with a

e Example—pH 7.42 with a $Paco_2$ of 30 mm Hg indicates a respiratory alkalosis with a metabolic acidosis.

Step 5—Correlate the above findings with clinical history and physical exam to arrive at the correct diagnosis (see Figure. 28.1 for select etiologies of respiratory acidosis and Table 28.3 for select causes of respiratory alkalosis).

Step 6—Treat appropriately (see discussion below).

ABBREVIATIONS
ABG: arterial blood gas (ABG)
$Paco_2$: partial pressure of carbon dioxide

TABLE 28.1 H+ Concentration and Corresponding pH

pH	$[H^+]$, mEq/L
7.00	100
7.10	79
7.20	63
7.30	50
7.40	40
7.50	32
7.60	25

TABLE 28.2 Expected $[HCO_3^-]$ Change in Acute and Chronic Respiratory Acid-Base Disorders (Assume a Baseline HCO_3^- of 24 mEq/L)

Acute respiratory acidosis	Increase in $[HCO_3^-] = \Delta Paco_2/10 \pm 3$

	Decrease in pH = 0.08 × [$\Delta Paco_2$/10]
Chronic respiratory acidosis (3-5 d)	Increase in [HCO_3^-] = 3 × [$\Delta Paco_2$/10][a] Decrease in pH = 0.03 × [$\Delta Paco_2$/10] to 0.08 × [$\Delta Paco_2$/10]
Acute respiratory alkalosis	Decrease in [HCO_3^-] = 2 × [$\Delta Paco_2$/10] Increase in pH = 0.08 × [$\Delta Paco_2$/10]
Chronic respiratory alkalosis	Decrease in [HCO_3^-] = 5 × [$\Delta Paco_2$/10] to 7 × [$\Delta Paco_2$/10] Increase in pH = 0.03 × [$\Delta Paco_2$/10] to 0.08 × [$\Delta Paco_2$/10]

[a]Some authors use 3.5 mEq/L for chronic respiratory acidosis.

$Paco_2$, partial pressure of carbon dioxide

DISCUSSION

Carbon dioxide is excreted in the lung by simple diffusion and depends on the constant movement of alveolar air. Normal pH is maintained through the equilibrium between cellular CO_2 production and minute ventilation (respiratory rate × tidal volume). Chemoreceptors in the brain sense changes in cellular metabolism by increases in $Paco_2$ and regulate respiratory drive by increases or decreases in tidal volume and respiratory rate. Disturbances in this equilibrium are the basis of the pathophysiology of respiratory acid-base disorders.

Quite simply, the pathophysiology of acute respiratory acidemia is due to alveolar hypoventilation, which results in hypercapnia and a pH less than 7.35. The approach to and differential diagnosis of hypercapnia is outlined in Chapter 8, An Approach to Respiratory Failure, Algorithm 8.1. Any component of the ventilatory mechanism may be involved, including both the central and peripheral nervous systems, neuromuscular junction, respiratory muscles, chest wall,

pleura, large airways, small airways, or lung parenchyma (see Figure 28.1).

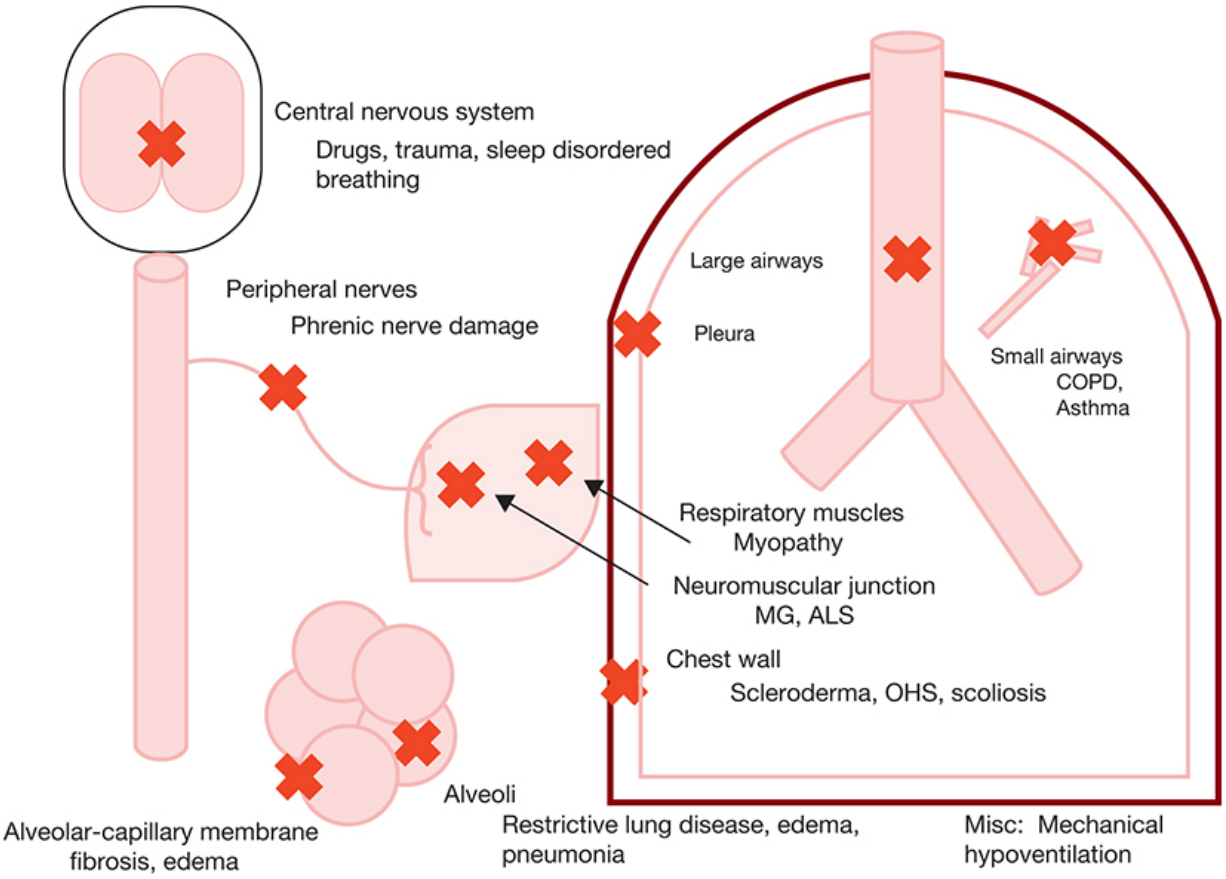

FIGURE 28.1 **Selected sites and causes of disease that can lead to hypoventilation.** ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease; MG, myasthenia gravis; OHS, obesity hypoventilation syndrome.

Correcting alveolar hypoventilation is the mainstay of treatment for acute respiratory acidosis and requires treating the underlying cause of hypoventilation. This may include bronchodilators (for patients with asthma and chronic obstructive pulmonary disease), reversal of medication/drug effects (in the case of an acute narcotic overdose), treatment of pulmonary edema, treatment of neuromuscular diseases, and mechanical ventilation (either via noninvasive positive pressure ventilation or via endotracheal intubation). Special caution is required when mechanically ventilating patients with acute

respiratory acidemia in the setting of compensated, chronic hypercapnia (chronically elevated $Paco_2$ with concomitant elevation of serum HCO_3^-), as rapid correction of the patient's respiratory acidosis can cause life-threatening metabolic alkalosis and alkalemia. Sodium bicarbonate is not recommended in respiratory acidosis as it may worsen hypercapnia and pulmonary edema, or induce a metabolic alkalosis and alkalemia. Small doses of sodium bicarbonate can be considered in cases of intractable hypercapnia with severe acidemia (pH <7.1).

Causes of respiratory alkalosis are listed in Table 28.3. The underlying pathophysiologic mechanism for each is alveolar hyperventilation. Acute respiratory alkalosis can be associated with either normal or increased alveolar-arterial oxygen gradient ($P[A\text{-}a]o_2$ gradient, or A-a gradient, discussed in more detail in Chapter 8, An Approach to Respiratory Failure). In patients with an elevated A-a gradient, the differential diagnosis is the same as for patients with hypoxemia with an elevated A-a gradient (see Algorithm 8.2). In patients with a normal A-a gradient, causes include hyperventilation due to central nervous system disorders, fever, severe anemia, hypoxemia from altitude, endocrine disorders, drugs, and iatrogenic hyperventilation in patients on mechanical ventilatory support.

TABLE 28.3 Select Causes of Respiratory Alkalosis

Normal $P(A\text{-}a)o_2$ Gradient	
Mechanical hyperventilation	Drugs Salicylates Progesterone Catecholamines
Central nervous system Psychogenic hyperventilation Fever Pain Encephalitis/meningitis	Tissue hypoxia High altitude Severe anemia

Tumors	
Pregnancy	Endotoxinemia
Hyperthyroidism	Cirrhosis
Elevated P(A-a)o_2 Gradient[a]	
$\dot{V}/\dot{Q}$ mismatch and stimulation of chest receptors Right to left shunt Pneumothorax Congestive heart failure	Pulmonary embolism Pneumonia Edema

P(A-a)o_2, alveolar-arterial oxygen gradient; $\dot{V}/\dot{Q}$, ventilation/perfusion.

[a]The differential diagnosis of respiratory alkalosis with an elevated alveolar-arterial oxygen gradient (P[A-a]o_2) is the same as hypoxemia with an elevated P(A-a)o_2 listed in Chapter 8, An Approach to Respiratory Failure, Algorithm 8.2.

Similar to acute respiratory acidosis, the treatment of acute respiratory alkalosis is directed at the underlying etiology. Causes of hypoxemia should be identified and treated. In mechanically ventilated patients, minute ventilation should be decreased by decreasing the respiratory rate and/or tidal volume. For psychogenic hyperventilation, reassurance and anxiolytics can be used.

Acetazolamide can be used to induce a metabolic acidosis to compensate for the acute respiratory alkalosis caused by high altitudes.

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SECTION VI ENDOCRINE DISORDERS

29 Thyroid Disorders

Amy E. Riek

Hyperthyroidism

Major clinical findings in hyperthyroidism are listed in Table 29.1. Notably, cardiac findings may be prominent, including tachycardia, atrial fibrillation, heart failure, and exacerbation of coronary artery disease. In rare cases, severe hyperthyroidism may be associated with systemic decompensation, often accompanied by fever and delirium, sometimes called “thyroid storm.” Precipitating factors can include cessation of antithyroid drugs, thyroidectomy, nonthyroidal surgery in unrecognized or undertreated hyperthyroidism, and acute illness.

TABLE 29.1 Major Clinical Findings in Hyperthyroidism

Common	Seen Primarily in Severe Hyperthyroidism
• Heat intolerance • Weight loss • Palpitations • Sinus tachycardia • Atrial fibrillation • Brisk tendon reflexes • Fine tremor • Lid lag • Proximal muscle weakness	• Heart failure • Exacerbation of coronary artery disease • Fever and delirium (“thyroid storm”)

The major causes of hyperthyroidism are listed in Table 29.2, with Graves disease (which may also cause proptosis) and nodular thyroid disease being the most common.

TABLE 29.2 Major Causes of Hyperthyroidism

Associated With Increased Radioactive Iodine Uptake

- Graves disease
- Toxic multinodular goiter
- Thyroid adenoma

Associated With Decreased Radioactive Iodine Uptake

- Iodine-induced hyperthyroidism (due to amiodarone or iodine-containing contrast media[a])
- Painless thyroiditis[b]
- Subacute thyroiditis[b]
- Factitious hyperthyroidism (ingestion of thyroid hormone)

Drugs Causing Variable Radioactive Iodine Uptake

- Checkpoint inhibitors[c]
- Lithium[c]
- Interferon alpha[c]
- Interleukin-2; other immunomodulatory drugs[c]

[a]Can cause both hyper- and hypothyroidism depending on the patients' underlying thyroid function and basal iodine consumption.

[b]Typically transient and may be followed by overt hypothyroidism.

[c]May cause a transient thyrotoxicosis before progressing to hypothyroidism.

When hyperthyroidism is suspected in a patient who is critically ill, plasma thyroid-stimulating hormone (TSH), free thyroxine (T_4), and free triiodothyronine (T_3) should be measured. Clinical hyperthyroidism suppresses TSH to below 0.1 mIU/L, making a normal plasma TSH level sufficient to exclude the diagnosis of hyperthyroidism, except in a very few rare conditions. Plasma TSH may also be suppressed to below normal by severe nonthyroidal illness (though rarely to undetectable) and by therapy with dopamine or high-dose glucocorticoids. Thus, a suppressed plasma TSH alone does not establish the diagnosis.

If plasma TSH is suppressed and plasma-free T_4 or free T_3 is elevated, the diagnosis of hyperthyroidism is established. However, if

plasma-free T_4 and free T_3 are not elevated, one of the other causes of suppressed plasma TSH listed earlier is more likely.

TREATMENT

The etiology of hyperthyroidism affects the choice of long-term therapy, but in patients who are critically ill, differential diagnosis can be deferred. Emergency therapy (Table 29.3) is indicated when hyperthyroidism exacerbates heart failure or an acute coronary syndrome, or when thyroid storm is present. This includes the rapid inhibition of thyroid hormone synthesis using a thionamide (propylthiouracil [PTU] or alternatively methimazole), inhibition of thyroid hormone secretion by iodine, and inhibition of the cardiovascular effects of hyperthyroidism by beta-adrenergic antagonists. Hydrocortisone is usually recommended because it inhibits T_4 conversion to T_3. At the same time, fever and any concomitant illness must be vigorously treated. Plasmapheresis/plasma exchange or emergency thyroidectomy can be considered in those with a poor response to usual therapies. While some authors have advocated treating amiodarone-induced hyperthyroidism with glucocorticoids alone, the regimen described earlier has a high success rate in managing this disorder.

TABLE 29.3 Emergency Therapy of Hyperthyroidism

Propylthiouracil (PTU) 500-1,000 mg PO load, then 250 mg PO q6h or alternatively, methimazole 60-80 mg PO qday in divided doses
Iodine (supersaturated potassium iodide, SSKI) five drops (250 mg) PO q6h (start 1 h after first dose of PTU)
Beta-antagonist, with the dose adjusted to control tachycardia; initially:
  Propranolol 60-80 mg PO q6h, or
  Esmolol 500 mcg/kg IV followed by 50 mcg/kg/min IV
Hydrocortisone 100 mg IV q8h

Plasma-free T_4 levels should be measured every 3 to 7 days. When free T_4 approaches the normal range, the doses of thionamide and iodine should be gradually decreased. Iodine can usually be stopped at the time of hospital discharge. Definitive therapy options, such as radioactive iodine (RAI) or near-total thyroidectomy for Graves disease or toxic multinodular goiter, can be considered after euthyroidism is achieved. If long-term thionamide therapy is chosen instead, methimazole is preferred due to its once-daily dosing and reduced risk of major side effects.

Hypothyroidism

Major clinical findings in hypothyroidism are listed in Table 29.4. Severe hypothyroidism may contribute to hypothermia, hypoventilation, bradycardia, hypotension, and hyponatremia in the setting of concomitant critical illnesses.

TABLE 29.4 Major Clinical Findings in Hypothyroidism

Common	Seen Primarily in Severe Hypothyroidism
• Cold intolerance • Fatigue • Somnolence • Constipation • Weight gain • Slow tendon reflexes • Nonpitting edema (myxedema) • Dry skin	• Hypothermia • Bradycardia • Hypoventilation • Hypotension • Hyponatremia • Pericardial or pleural effusion

The major causes of hypothyroidism are listed in Table 29.5. More than 90% of cases are primary hypothyroidism, most often iatrogenic

or due to chronic autoimmune thyroiditis. Any pituitary or hypothalamic disorder can cause secondary hypothyroidism, although these disorders are usually clinically apparent because of other manifestations.

TABLE 29.5 Major Causes of Primary Hypothyroidism

- Chronic lymphocytic thyroiditis (Hashimoto disease)
- Iatrogenic (after radioactive iodine therapy or thyroidectomy)
- Drugs
- Iodine excess (eg, amiodarone, iodine-containing contrast media[a])
- Checkpoint inhibitors[b]
- Lithium[b]
- Interferon alpha[b]
- Interleukin-2; other immunomodulatory drugs[b]

[a]Can cause both hyper- and hypothyroidism depending on the patients' underlying thyroid function and basal iodine consumption.
[b]May cause a transient thyrotoxicosis before progressing to hypothyroidism.

When hypothyroidism is suspected in a patient who is critically ill, plasma TSH and free T_4 should be measured. Even mild primary hypothyroidism causes an elevation of plasma TSH, so a normal plasma TSH excludes this diagnosis. Plasma TSH values exceeding 20 mIU/L establish the presence of primary hypothyroidism. While milder elevations of plasma TSH are usually associated with primary hypothyroidism, they may also occur transiently during recovery from severe nonthyroidal illness.

If plasma-free T_4 is low and plasma TSH is not elevated, the patient may have secondary hypothyroidism. However, in patients who are critically ill, this pattern of test results is more likely indicative of functional suppression of TSH and T_4 secretion by the nonthyroidal illness. If the patient has clinical findings that may be due to hypothyroidism, empiric treatment with T_4 should be started, and the diagnosis should be reassessed after recovery. Otherwise,

the patient can be observed with periodic measurement of plasma TSH and free T_4 to determine whether the abnormalities resolve with recovery.

TREATMENT

Emergency therapy of hypothyroidism (Table 29.6) is indicated if the patient exhibits clinical signs that could be contributed by hypothyroidism, such as bradycardia, hypoventilation, hypothermia, or hypotension. Each of these abnormalities should also be treated in the standard fashion, since they are rarely due to hypothyroidism alone. Vital signs and cardiac rhythm should be monitored, as the treatment may exacerbate underlying heart disease. Stress dose hydrocortisone should be given prior to repletion of thyroid hormone because adrenal failure may be associated with chronic autoimmune thyroiditis, and adrenal crisis can be precipitated by the administration of thyroid hormone in the absence of adequate glucocorticoid.

TABLE 29.6 Emergency Therapy of Hyperthyroidism

Thyroxine, consider loading dose of 200-400 mcg IV, then 1.2 mcg/kg IV q24h until oral intake is possible
Hydrocortisone 100 mg IV q8h

No clinical trials have determined the optimum method for the emergency treatment of hypothyroidism. Nevertheless, this method rapidly alleviates T_4 deficiency while minimizing the risk of adverse events. Currently, there is no evidence supporting the treatment of the functional suppression of TSH and T_4 by nonthyroidal illness.

SUGGESTED READINGS

Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol.* 2015:3(10):816-825.

30 Adrenal Insufficiency in Critical Illness

Nguyet Nguyen

An increase in circulating and tissue corticosteroid levels during critical illness is an important adaptive response. Normally, severe illness and stress stimulate the hypothalamic-pituitary-adrenal (HPA) axis, causing the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH or corticotropin), with ACTH causing increased cortisol production by the adrenal cortex's zona fasciculata. With acute illnesses such as severe infection, trauma, and burns, there is an increase in cortisol production by as much as a factor of 6. Normally, circulating cortisol is bound to corticosteroid-binding globulin (CBG) and albumin, with less than 10% in the free, bioavailable form. During acute illness, however, CBG and albumin levels decrease by as much as 50%, with unbound cortisol levels increasing. Although it is the unbound cortisol that is physiologically active, current laboratory assays only measure total cortisol. In a healthy, unstressed person, the HPA axis undergoes diurnal variation, but this is lost in critical illness. The major physiologic actions of circulating cortisol include increasing blood sugar levels; facilitating the delivery of glucose to cells during stress; facilitating normal cardiovascular reactivity to angiotensin II, epinephrine, and norepinephrine; contributing to the maintenance of cardiac contractility, vascular tone, and blood pressure; and anti-inflammatory and immunosuppressive effects.

Chronic adrenal insufficiency (Addison disease) is a rare cause of intensive care unit (ICU) admission and is distinct from the HPA axis dysfunction that occurs during critical illness, which has been termed *critical illness-related corticosteroid insufficiency* (CIRCI). CIRCI is

characterized by an inappropriately low increase in cortisol during acute illness, also referred to as *relative adrenal insufficiency*. It is mediated in part by inflammatory cytokine inhibition of (a) CRH and ACTH release, (b) adrenal cortisol synthesis, and (c) glucocorticoid receptor translocation and transcription. In addition to CIRCI, adrenal insufficiency in critical illness may also be separated into two categories: *primary,* if it is due to adrenal gland dysfunction, or *secondary,* if it is caused by central disruption of CRH or ACTH release. Causes of primary adrenal insufficiency in acute illness include direct injury to the adrenal glands from trauma, infarction, infection, malignancy, and hemorrhage; drug-induced suppression of cortisol synthesis; and autoimmune adrenalitis. Secondary causes include discontinuation of exogenous corticosteroids in patients on chronic immunotherapy, central nervous system malignancies, and head trauma. Causes of adrenal insufficiency are listed in Table 30.1.

TABLE 30.1 Causes of Adrenal Insufficiency

Cause	Example
Infection	Sepsis/septic shock
	HIV
	Cytomegalovirus
	Staphylococcus aureus, toxin-producing strain
	Fungal disorders (histoplasmosis, blastomycosis, cryptococcus)
	Tuberculosis
Medications	Suppressing release of corticotropin-releasing hormone from the hypothalamus and pituitary:
	Corticosteroids

Cause	Example
	Megestrol acetate
	Inhibition of enzymes involved in cortisol synthesis:
	Etomidate
	Ketoconazole
	Metyrapone
	Increased metabolism of cortisol:
	Rifampin
	Phenytoin
Malignancy	Adrenal metastases
Adrenal hemorrhage	Secondary to shock
	Anticoagulation
	Meningococcemia (Waterhouse-Friderichsen syndrome)
	Disseminated intravascular coagulation
	Antiphospholipid syndrome
Autoimmune	Addison disease
Hypothalamic and	Resulting in secondary adrenal insufficiency:
pituitary disorders	Infection
	Pituitary tumor or metastases
	Infiltrative disorders (sarcoidosis, histiocytosis)

Cause	Example
	Postpartum pituitary necrosis
	Trauma (blunt, radiation, surgical)

HIV, human immunodeficiency virus.

Signs and symptoms of corticosteroid insufficiency resulting from HPA dysfunction are listed in Table 30.2. In preexisting hypoadrenalism, these findings may be present before the onset of acute illness. However, in critically ill patients, adrenal insufficiency should be suspected in all patients with hypotension that is unresponsive to intravenous (IV) fluid administration and vasopressor support.

TABLE 30.2 Signs and Symptoms of Adrenal Insufficiency

Sign	Symptoms
Cardiovascular	Hypotension that is usually not responsive to fluid administration requiring use of vasopressors; hyperdynamic hemodynamic profile is common; hypotension refractory to catecholamines; tachycardia unless severe hypothyroidism is also present.
Metabolic/electrolyte	Hypoglycemia, hyponatremia, hyperkalemia, fever
Hematologic	Eosinophilia and anemia
Neuromuscular	Weakness, fatigue, myalgia, arthralgia, headache, memory impairment, depression
Gastrointestinal	Anorexia, diarrhea, nausea, salt craving, weight loss
Cutaneous	Vitiligo, alopecia

Although it is well documented that acute illness increases cortisol through stimulation of the HPA axis, it is less clear what defines an adequate stress response to acute illness. In addition, although CIRCI should be considered in all critically ill patients, most of the studies have focused on patients with sepsis and septic shock. Previous studies have suggested that random serum cortisol levels greater than 25 to 34 mcg/dL in critically ill patients make relative adrenal insufficiency unlikely. However, recent studies have suggested that random cortisol measurements may have limited utility in the diagnosis of adrenal insufficiency, except in patients with baseline cortisol less than 10 to 15 mcg/dL, and have highlighted the diagnostic value of a cortisol increase of less than or equal to 9 mcg/dL 60 minutes after stimulation with 250 mcg of IV cosyntropin (synthetic ACTH), indicating adrenal insufficiency likely in critical illness.

In a prospective inception cohort study performed by Annane et al in 2000 of 189 patients with septic shock, it was noted that an intermediate or poor prognosis occurred in patients with a cortisol increase in response to cosyntropin of less than or equal to 9 mcg/dL, with the highest mortality found in those patients who, in addition to a cosyntropin response of less than or equal to 9 mcg/dL, had an initial cortisol level of greater than 34 mcg/dL. Another study by Annane et al in 2006 of 101 patients with sepsis, 41 patients without sepsis, and 32 healthy controls employed the overnight metyrapone stimulation test to investigate the diagnostic value of various markers of adrenal function and found that adrenal insufficiency was likely if the baseline cortisol level was less than 10 mcg/dL or change in cortisol after cosyntropin was less than or equal to 9 mcg/dL, and unlikely when cosyntropin stimulated cortisol levels were greater than or equal to 44 mcg/dL and the change in cortisol after cosyntropin was greater than or equal to 16.8 mcg/dL. These diagnostic values were explored further in 2007 by Lipiner-Friedman et al in the retrospective arm of the CORTICUS study group. This retrospective multicenter cohort study included 477 patients with sepsis and septic shock who had undergone an ACTH stimulation test on the first day of sepsis and found that random cortisol levels

greater than or equal to 15 mcg/dL, regardless of the cutoff, were not independent predictors of shock reversal, hospital mortality, or survival duration. However, patients with a baseline cortisol level less than 15 mcg/dL or change in cortisol level less than or equal to 9 mcg/dL after cosyntropin had a longer duration of shock and a shorter survival time. Corticosteroids were used to treat 44% of patients and were associated with a strong reduction in the risk of dying (OR [odds ratio], 0.21; 98% CI [confidence interval], 0.08-0.52). Measuring serum cortisol 30 and 60 minutes after cosyntropin added no significant diagnostic value to checking cortisol at 60 minutes alone.

Randomized studies have been performed to determine if corticosteroid replacement therapy is beneficial in patients with varying diagnostic definitions of adrenal insufficiency. In a placebo-controlled, randomized, double-blind study by Annane et al in 2002, 300 patients with septic shock were randomized to receive hydrocortisone 50 mg every 6 hours and fludrocortisone 50 mcg once daily for 7 days, or placebo, after undergoing a 250 mcg cosyntropin test. Of the 229 patients with relative adrenal insufficiency (115 placebo and 114 corticosteroid), defined as an increase after cosyntropin of less than or equal to 9 mcg/dL, there was significantly reduced mortality (73 patients vs 60 patients, *P* = .02) and withdrawal of vasopressor therapy within 28 days (46 patients vs 65 patients, *P* = .001) in the patients treated with corticosteroid, without increasing adverse events. In the 70 patients who had a cosyntropin response greater than or equal to 9 mcg/dL, corticosteroid replacement therapy had no significant effect on the same outcomes and no trend toward efficacy. The APROCCHSS trial by the same group in 2018, with 1,241 patients randomized to the same corticosteroid dose and duration as mentioned earlier or placebo, showed decrease in mortality at 90-day (43.0% [264 of 614 of treatment group] and 49.1% [308 of 627 placebo group], *P* = .03) and 180-day (46.6% of treatment group and 52.5% placebo group, *P* = .04) time points.

However, the CORTICUS study found no benefit to treating patients with septic shock, including the subgroup with a cosyntropin

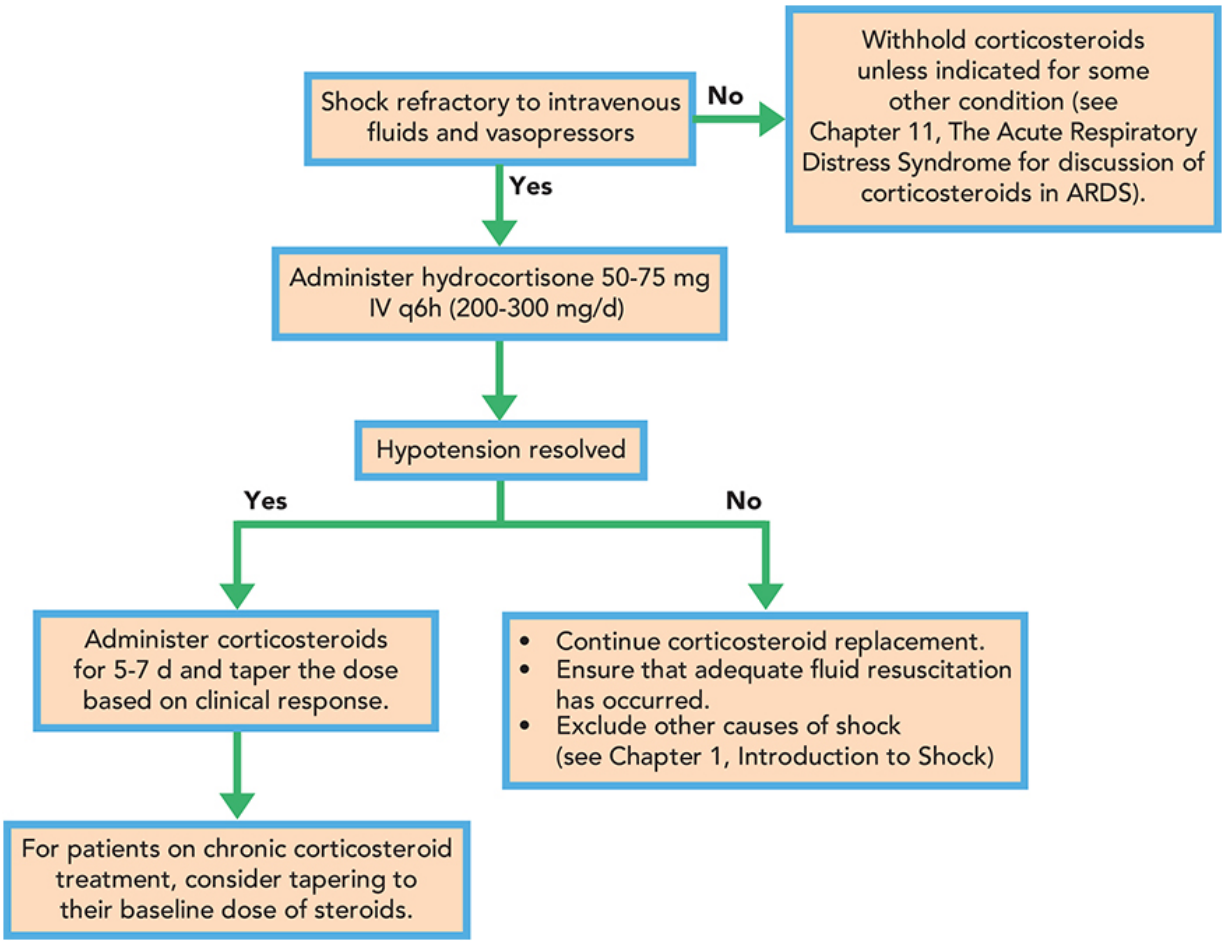
response less than or equal to 9 mcg/dL. This study differed from the initial randomized study by Annane in 2002 in that patients in the CORTICUS study were randomized up to 72 hours after the onset of septic shock rather than within 8 hours; patients in the CORTICUS study included those with sepsis and septic shock rather than septic shock alone (ie, could be included in the study without hypotension requiring vasopressors), received 11 days of corticosteroid replacement rather than 7 days, and were not given fludrocortisone. In addition, the CORTICUS study lacked clinical equipoise resulting in a selection bias whereby patients least likely to benefit from corticosteroids were enrolled in the study. The multicenter ADRENAL trial enrolled 3,658 patients with septic shock, continuous infusion of 200 mg hydrocortisone daily for 7 days showed a faster resolution of shock, decreased time to discharge from ICU, decreased time of initial mechanical ventilation, and decreased number of blood transfusions but did not affect the mortality rate at 90-day (511 of 1,832 [27.0%] treatment group, 526 of 1,826 [28.8%] placebo group, P = .50) or 28-day (410 of 1,841 [22.3%] treatment group, 448 of 1,840 [24.3%] placebo group, P = .13).

Glucocorticoids, however, may not be appropriate for all critically ill patients as highlighted in a case-control study by Britt et al in 2006 in 100 patients (six with septic shock) in a burn trauma ICU who received steroids, compared with 100 matched control patients, showing that corticosteroid use was associated with increased infection rates, increased ICU and ventilator duration, and a trend toward increased mortality.

Thus, although our understanding of relative adrenal insufficiency in the critically ill continues to evolve, nearly all evidence agree that adrenal insufficiency is likely when the baseline cortisol is less than 10 to 15 mcg/dL in critically ill patients and that cosyntropin stimulation testing may have additional diagnostic value in identifying which patients are likely to respond to corticosteroid replacement, at least in the setting of volume unresponsive hypotension in patients with septic shock. However, given the often unreliable nature of cortisol concentrations in blood and their response to cosyntropin stimulation, we recommend that critically ill patients with refractory

septic shock unresponsive to IV fluids and vasopressor support be managed as illustrated in Algorithm 30.1. Patients should be started on hydrocortisone (200-300 mg/d) for 5 to 7 days. Once treatment is initiated, the cause of adrenal insufficiency can be explored further. Many patients with adrenal insufficiency related to critical illness can be expected to regain normal function of the HPA axis with recovery from their illness. Some experts, however, still use the random cortisol alone, feeling that adrenal insufficiency is unlikely when the random cortisol is greater than or equal to 25 mcg/dL and that corticosteroids can be withheld in that setting. While older meta-analyses of corticosteroid therapy in critical illness suggest a decrease in mortality with treatment, especially in severely ill patients with septic shock, newer meta-analyses show minimal or no mortality benefits. However, these same meta-analyses suggest that administration of corticosteroids improved rates of shock reversal, decreased duration of mechanical ventilation, decreased duration of ICU stay, and decreased length of hospital stay. Therefore, corticosteroid replacement should be provided to all patients with refractory septic shock that is not responsive to IV fluids and vasopressors.

ALGORITHM 30.1 **Therapeutic Approach to Relative Adrenal Insufficiency in the Critically Ill Patient**


Shock refractory to intravenous fluids and vasopressors
No
Withhold corticosteroids unless indicated for some other condition (see Chapter 11, The Acute Respiratory Distress Syndrome for discussion of corticosteroids in ARDS).
Yes
Administer hydrocortisone 50-75 mg IV q6h (200-300 mg/d)
Hypotension resolved
Yes
No
Administer corticosteroids for 5-7 d and taper the dose based on clinical response.
Continue corticosteroid replacement.
Ensure that adequate fluid resuscitation has occurred.
Exclude other causes of shock (see Chapter 1, Introduction to Shock)
For patients on chronic corticosteroid treatment, consider tapering to their baseline dose of steroids.

SUGGESTED READINGS

Annane A, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004;329:480-489.

Meta-analysis of 16 randomized and quasi-randomized trials involving 2,063 patients with severe sepsis and septic shock showing that long courses (≥5 days) with low-dose corticosteroids (≤300 mg hydrocortisone or equivalent) reduced 28-day and hospital mortality.

Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA.* 2009;301:2362-2375.

A systematic review of 17 trials with 12 trials investigating prolonged low-dose corticosteroid therapy, with the latter subgroup suggesting a beneficial effect in terms of short-term mortality.

Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev.* 2015;12:CD002243.

31 Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Sarah Singer, Tracy Trupka, Marin H. Kollef, and Gary S. Tobin

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are life-threatening hyperglycemic complications of diabetes mellitus (DM) and common reasons for admission to the intensive care unit (ICU). The incidence of DKA is approximately 61.6 cases per 10,000 admissions resulting in a total of more than 220,000 hospitalizations per year with an ongoing upward trend. Furthermore, DKA admissions account for over 6.7 billion dollars in health care costs in the US annually. The annual incidence of HHS is lower than DKA and accounts for less than 1% of primary diabetic admissions. The mortality rate in DKA has declined consistently over time and is now reported to be less than 1%, although it remains greater than 5% in older patients or those with other life-threatening comorbidities. However, in HHS, the mortality rate is at least 10-fold higher than DKA, ranging from 10% to 20%. Notably, mortality in HHS is most often due to the underlying condition that precipitated the decompensation rather than the metabolic derangements related to the hyperglycemic state. Even more detrimental outcomes are observed at extremes of age and with the presence of coma, hypotension, and severe comorbidities. The precipitating factor is most commonly an infection (most commonly pneumonia [40%-60%] and urinary tract infections [5%-16%]). Other common causes include inadequate insulin treatment or noncompliance, new-onset DM, cardiovascular events, cerebral vascular accident (CVA), pancreatitis, drugs/alcohol abuse, pulmonary embolism, trauma, and pregnancy. Medications such as corticosteroids, pentamidine, thiazide diuretics, and sympathomimetic agents may also contribute

to the development of DKA/HHS due to their impacts on carbohydrate metabolism. DKA most commonly occurs in patients with type 1 DM, but does occur in patients with type 2 DM (as high as 1/3 of DKA cases). HHS is typically confined to patients with type 2 DM. Severity of the condition at the time of presentation is often exacerbated by limited intake of water in the older or chronically ill. DKA and HHS are the result of insulin deficiency in patients with DM. In both disorders, insulin deficiency causes increased hepatic glycolysis, gluconeogenesis, and impaired glucose utilization by peripheral tissues leading to hyperglycemia, which, in turn, causes an osmotic diuresis. Table 31.1 highlights the differences between DKA and HHS.

TABLE 31.1 Initial Laboratory Values in DKA and HHS

	DKA			
Value	**Mild**	**Moderate**	**Severe**	**HHS**
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7-7.24	<7	>7.30
Serum bicarbonate (mEq/L)	15-18	10-14	<10	>18
Urine and serum ketones	Positive	Positive	Positive	Trace/small
Serum osmolarity (mOsm/L)	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma
Sodium (mmol/L)	125-135	125-135	125-135	135-145

	DKA			
Value	**Mild**	**Moderate**	**Severe**	**HHS**
Potassium (mmol/L)	Normal to ↑	Normal to ↑	Normal to ↑	Normal
Creatinine (mg/dL)	Slight ↑	Slight ↑	Slight ↑	Moderate ↑

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

Diabetic Ketoacidosis

DKA is characterized by hyperglycemia (blood glucose [BG] typically 250-800 mg/dL), anion gap metabolic acidosis (arterial pH ≤7.3), and ketosis (positive urine and plasma ketones), along with dehydration and electrolyte abnormalities in varying degrees. Common ketone assays use nitroprusside, measuring acetoacetate and acetone, but not beta-hydroxybutyrate which requires a separate assay. Prominent presenting symptoms include nausea/vomiting, abdominal pain, labored breathing (Kussmaul respirations), and polyuria. A mixed acid-base disorder may also be present, such as a concomitant severe contraction metabolic alkalosis elevating the serum bicarbonate level, masking the underlying metabolic acidosis.

In patients with DKA, the absolute lack of insulin causes an increase in counterregulatory hormones (cortisol, growth hormone, catecholamines, and glucagon), which impair glucose utilization in tissues, increase gluconeogenesis, and hasten glycogenolysis. Both insulin deficiency and the release of counterregulatory hormones promote lipolysis in adipose tissue and the release of free fatty acids. In the liver, the free fatty acids are converted to ketones. These patients suffer from metabolic acidosis due to these circulating ketoacids. Ketone bodies and hyperglycemia contribute to the osmotic diuresis, resulting in a loss of sodium and potassium. Although initial laboratory values are variable (often with a state of apparent hyperkalemia due to potassium efflux into the extracellular

space in the acidotic environment), total body sodium and potassium are depleted.

While prompt management of DKA is essential, finding and treating the precipitating cause should not be delayed or neglected. Blood, urine, and sputum cultures, chest x-ray, electrocardiogram (ECG), and empiric treatment based on clinical suspicion should be part of the initial management of DKA. One should further evaluate the cause of abdominal pain if this symptom does not resolve with correction of the dehydration and metabolic acidosis.

Treatment of DKA requires reversal of hyperglycemia by administering insulin and replacing the circulating and total body volume and electrolyte deficits (Algorithm 31.1). Fluid deficits in DKA can exceed 6 L. Mainstay of therapy consists of normal saline (NS) boluses for acute volume resuscitation, followed by either NS if corrected sodium is low or 1/2 NS if corrected sodium is normal or elevated to replace the remaining fluid deficit. Later, 5% dextrose-containing fluids are continued from the time the glucose falls below 250 mg/dL, until the anion gap normalizes and the patient is able to tolerate oral intake. Special consideration should be taken in patients with renal or cardiac dysfunction to avoid fluid overload. Insulin should be given as an intravenous (IV) bolus, followed by continuous infusion. Hyperglycemia resolves faster than acidosis, and supraphysiologic insulin doses are needed to overcome hyperglycemia-induced insulin resistance to achieve euglycemia. After euglycemia is achieved, insulin is still required to drive peripheral ketone use, resolving the remaining acidosis. Therefore, the BG should be kept between 150 and 200 mg/dL with 5% dextrose until the anion gap is closed. Intermediate- or long-acting subcutaneous (SC) insulin must be given 1 to 2 hours before insulin drip discontinuation. Failure to administer subcutaneous insulin properly can lead to rebound hyperglycemia and recurrence of DKA. The patient should be able to tolerate PO (oral) fluids, and dextrose-containing IV fluids should be stopped at that time.

ALGORITHM 31.1 Management of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

INSULIN TREATMENT

1. Bolus 0.1-0.15 U/kg regular insulin intravenously (IV) (Subcutaneous [SC]/intramuscular [IM] can be given if no IV access.)
2. Start continuous IV insulin infusion via an infusion pump.
   Standard infusion is 100 U **regular human insulin** (IV $t^1/_2$ 5-9 min) in 100 mL 0.9% NaCl.
   For **DKA,** start at 0.1 U/kg/h.
   For **HHS,** start at 0.05 U/kg/h; delay insulin in **HHS** until at least 1 L NS infused.

BLOOD GLUCOSE MONITORING

1. Check initial blood glucose (BG) every 1 h. **Goal decrease in BG is 50-75 mg/dL/h.**
2. Once stable (three consecutive values decreased in target range), change BG monitoring to every 2 h. Resume every 1 h BG monitoring for each change in the insulin infusion rate (see below).
3. Add dextrose 5% to IV fluids when BG <250 mg/dL.
   For **DKA, goal BG is 150-200 mg/dL until anion gap closed.**
   For **HHS, goal BG is 250-300 mg/dL until mental status improves.**

CHANGING THE INSULIN INFUSION RATE

1. ↓ IV insulin by 50%/h if BG decreases by >100 mg/dL/h in any 1-h period.[a]
2. ↑ insulin drip by 50%/h if change in BG is <50 mg/dL/h.
3. For **DKA and HSS**, when BG decreases to 250 mg/dL, insulin infusion may need to be decreased 50% to maintain glucose at target levels (see Blood Glucose Monitoring above).

Start SC insulin when:

1. Anion gap closed (DKA)
2. Serum bicarbonate increases to >15 mEq/L (DKA)
3. Patient able to eat
4. Mental status improves (HHS)

Stop the insulin drip after all of the following are done[b]:

1. Give short-acting insulin (aspart or lispro) SC at twice the hourly IV rate (eg, if IV rate is 5 U/h, give 10 U short-acting insulin SC).
2. Give long-acting insulin (NPH or glargine) SC at 0.2-0.3 U/kg (divided every 8 to 12 hours for NPH), or home insulin dose.
3. Ensure patient has a meal and is eating.

FLUID MANAGEMENT*

Fluid replacement varies based on age, weight, hemodynamics, and comorbidities. A reasonable approach follows:

1. **Replace intravascular volume**
   Give 1 L 0.9% NaCl over 30-60 min. Give an additional 1-2 L every 30-60 min until hemodynamically stable and urine output increased.
2. **Replace total body water deficit**
   Change to 0.45% NaCl and infuse at 150-500 mL/h.
   When BG <250 mg/dL, add dextrose 5% and decrease to 100-200 mL/h.

*Fluid is replaced over 12-24 h and patients are generally depleted 3-6 L in DKA and 8-12 L in HHS. Monitor urine output, heart rate, blood pressure, and respiratory status. Care must be taken in patients with congestive heart failure and kidney disease.

ELECTROLYTE MANAGEMENT

1. Check basic metabolic panel (BMP), arterial blood gas, magnesium (Mg^{2+}), and phosphorus (PO_4^{3-}).
2. Repeat BMP, Mg, PO_4^{3-} every 2-4 h depending on degree of electrolyte imbalance.

Potassium (K^+)

K^+ ≥5.5 mEq/L: leave potassium supplement out of IVF.
K^+ 4-5.4 mEq/L: add 20 mEq KCl/L to IVF.
K^+ 3-3.9 mEq/L: add 40 mEq KCl/L to IVF.
K^+ <3 mEq/L: add 60 mEq KCl/L to IVF.
In DKA, if initial K^+ is <3.3 mEq/L, **DO NOT** give IV insulin until the serum K^+ is supplemented to >3.3 mmol/L due to the risk of severe hypokalemia.

Sodium (Na^+)

Hypoglycemia causes an artifactually low serum sodium, and the correct value must be calculated. Corrected Na^+ = Measured Na^+ [mmol/L] + (1.6 [Measured BG (mg/dL) – 100]/100)

Na^+ replaced with IV Fs initially as 0.9% NaCl for first 1-3 L and then as 0.45% NaCl (see "Fluid Management" section).

Bicarbonate (HCO_3^-)

Usually in DKA only.

Replacement generally not necessary as insulin will reverse the HCO_3^- deficit with its inhibition of lipolysis.

Consider HCO_3^- in the following situations (see Chapter 25; metabolic acidosis):

1. Severe acidosis with pH <7 (the HCO_3^- should be stopped once the pH is >7.1)
2. Severe loss of buffering capacity when serum HCO_3^- <5-10 mEq/L
3. Acidosis-induced cardiac or respiratory distress
4. Severe hyperkalemia

Magnesium and Phosphorus

Severe hypomagnesemia and hypophosphatemia are not common complications

Severe hypomagnesemia and hypophosphatemia are not common complications of DKA and HHS (see Chapter 29 if they occur) and supplementation is usually not necessary.

PRECIPITATING FACTOR TREATMENT

The cause of the DKA or HHS should be sought and treated. Common precipitants include missed insulin therapy, infections such as pneumonia, sepsis, and urinary and upper respiratory tract infections, trauma, myocardial infarction, pregnancy, or as the initial presentation of DM.

ABBREVIATIONS

DKA:	diabetic ketoacidosis	IVF,IV:	intravenous fluid
HHS:	hyperosmolar hyperglycemic state	NPH:	neutral protamine Hagedorn.
IV:	intravenous		

In patients with mild and moderate DKA, SC rapid-acting insulin (lispro or aspart) administered every 1 to 2 hours may be used as an alternative to IV insulin regular in the non-ICU setting. However, this is a less reliable method to achieve the insulin levels needed in seriously ill patients. Patients with severe DKA, hypotension, or factors that may reduce SC absorption (eg, anasarca) should receive IV insulin regular and be admitted to the ICU. In adults, the BG should be decreased by 50 to 100 mg/dL/h. Decreasing the BG more than 75 to 100 mg/dL/h can cause an osmotic encephalopathy (0.3%-1% of DKA in children, extremely rare in adults). Glucose lowering in the first 2 hours may be more rapid as a result of initial volume expansion.

Insulin and IV fluids will correct the acidosis in patients with DKA but can rapidly produce hypokalemia, as potassium shifts intracellularly. The patient is total body potassium deficient at presentation, even if serum potassium is elevated (caution in concomitant chronic kidney disease). Successful treatment requires frequent monitoring and decision-making based on the patient's clinical condition and laboratory data as it becomes available.

Hyperosmolar Hyperglycemic State

HHS is characterized by hyperglycemia (BG typically 600 to >1,200 mg/dL), hyperosmolarity (serum osmolarity 320-380 mOsm/L), pronounced dehydration (hemodynamic instability, prerenal azotemia, decreased urine output), and neurologic sequelae ranging from mild lethargy to coma. HHS has an insidious onset, typically over weeks, with patients experiencing polyuria, polydipsia, weight loss, and neurologic changes, including fatigue, confusion, or coma. Even in the absence of exogenous insulin, there is typically enough intrinsic insulin production by beta cells to suppress hepatic lipoprotein lipase and ketoacid production. As a result, HHS lacks the metabolic acidosis prominent in DKA; however, small amounts of ketoacids may still be present from concomitant alcoholic or starvation ketosis. In HHS, the hyperglycemia is more pronounced than in DKA, resulting in greater diuresis (average fluid deficit of 9 L vs 6 L in DKA). The resulting dehydration impairs renal function, decreasing glucose excretion, and worsening hyperglycemia. IV insulin should not be given until fluid resuscitation with 1 to 2 L of NS has been completed to prevent rapid hyperglycemia correction and hemodynamic collapse from intracellular fluid shifts. Patients with HHS are often more responsive to insulin than patients with DKA and a lower dose is often used; however, prospective data evaluating treatment of HHS are lacking. Institutional low-dose insulin protocols developed for the treatment of DKA are often utilized in the treatment of HHS and appear to be effective. Generally, the BG should be kept slightly higher, generally between 250 and 300 mg/dL, to allow gradual correction of intracranial fluid shifts. These levels should be maintained until the patient's mental status improves. When this happens, IV insulin can be converted to SC insulin as listed in Algorithm 31.1. Failure to give SC insulin when the IV insulin is stopped can result in rebound hyperglycemia with worsening mental status in HHS. Special attention should also be placed on maintaining appropriate serum potassium levels. Hyperosmolarity and insulin deficiency often lead to potassium shifts

from the intracellular space to the plasma. When hydration and insulin therapies are administered, serum potassium levels often rapidly fall, requiring repletion. Mental status has been shown to correlate with elevated serum osmolality at presentation but not with acidosis. Stupor or coma while serum osmolality is less than 320 mOsm/L warrants immediate consideration of other causes of altered mental status.

Cerebral Edema

While hypoglycemia is the most common complication of treatment for DKA/HHS, cerebral edema (CE), occurring in 0.3% to 1% of cases, remains a far more serious complication. DKA complicated by CE carries a mortality rate of 20% to 30% and is responsible for approximately 50% to 90% of deaths in children with diabetes. Symptoms include headache, altered mental status, or a sudden deterioration in mental status after an initial improvement. Bradycardia, hypertension, and papilledema can be observed. CE usually develops within the first 12 hours after treatment has started but can occur before treatment has begun or, uncommonly, may develop as late as 24 to 48 hours after the start of treatment. The mechanisms behind CE in DKA remain controversial but are thought to include cytotoxic effects from metabolic derangements and hypoxic injury, vasogenic injury, and resulting osmotic shifts. Retrospective studies have linked CE with excessive, low-tonicity fluid repletion and rapid decline in BG. More recent studies, however, have failed to demonstrate an association between methods of fluid repletion and the incidence of CE. Given the paucity of the data, providers should continue to be aware of the rate of fluid repletion and rapid shifts in osmolality when treating DKA/HHS. Effective osmolality and water deficit can be calculated to replete at an appropriate rate (Algorithm 31.1). If serum sodium does not rise during volume resuscitation, it may be indicative of excess hydration with free H_2O. Prompt recognition and treatment with IV mannitol

and hypertonic saline are essential to prevent neurologic sequelae. Computed tomography imaging may show the presence of CE. Morbidity and mortality are high once CE is recognized (Table 31.2).

TABLE 31.2 Treatment of Cerebral Edema Complicating DKA or HHS

Initiate treatment as soon as cerebral edema is clinically suspected.
Give mannitol 0.5-1 g/kg IV over 20 min and repeat if there is no initial response in 30 min to 1 h.
Immediately reduce the rate of fluid administrated by 1/3.
Hypertonic saline (3%), 5-10 mL/kg over 30 min, may be an alternative to mannitol, especially if there is no initial response to mannitol.
Elevate the head of the bed.
Intubation for airway protection and impending respiratory failure.
Hyperventilation to a P_{CO_2} <22 mm Hg has been associated with poor outcomes and is not recommended.
After treatment for cerebral edema is initiated, a brain CT should be obtained to rule out other possible causes of intracerebral deterioration, especially thrombosis or hemorrhage.

CT, computed tomography; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; IV, intravenous; P_{CO_2}, partial pressure of carbon dioxide.

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32 Glucose Control in the Intensive Care Unit

Sarah Singer Marin H. Kollef, Paulina Cruz Bravo, and Garry S. Tobin

Hyperglycemia is a common occurrence in up to 90% of patients in the intensive care unit (ICU), accounting for both patients with and without diabetes. Factors contributing to hyperglycemia in critically ill patients include increased counterregulatory hormones (cortisol and glucagon), hepatic insulin resistance, decreased physical activity with resultant decrease in insulin-stimulated glucose uptake in the heart and skeletal muscle, glucocorticoid therapy, dextrose-containing intravenous (IV) fluids, and dense caloric enteral and parenteral nutrition. Numerous observational studies have shown that hyperglycemia is an independent risk factor for morbidity and mortality in patients in the medical, surgical, neurology, and cardiac ICUs, including postoperative cardiac and general surgery patients, patients with acute myocardial infarction and stroke, and general medicine patients.

Previous single-center randomized trials have suggested that treating hyperglycemia in critically ill patients could reduce morbidity and mortality. However, the patients that benefit the most from treatment and the optimal glucose targets were unclear from those studies. More recently, multicenter trials have demonstrated that hypoglycemia and intensive glycemic control were associated with adverse outcomes including increased hospital mortality. The following discussion addresses the current evidence, recommendations, and areas of uncertainty regarding glucose control in the ICU.

Trials

The seminal trial that evaluated the treatment of hyperglycemia in critically ill patients was published by Van Den Berghe et al in 2001 (Leuven I). The study randomized 1,548 intubated surgical ICU patients to receive intensive glycemic control (target blood glucose [BG] of 80-110 mg/dL, *n* = 765) or standard of care (target BG 180-200 mg/dL, *n* = 783). The study found that the ICU mortality rate was 42% lower (8% vs 4.6%, *P* < .04) in the intensive glycemic control group, with a significant benefit in patients who remained in the ICU for more than 5 days. The reduction in mortality was attributed to a decrease in the development of multiorgan failure with sepsis. Notably, the majority of patients enrolled in the study received cardiac surgery, suggesting improved outcomes with intensive glycemic control in this population.

In 2006, Van Den Berghe et al conducted a follow-up study (Leuven II) in 1,200 medical ICU patients (16.9% with known diabetes). Patients were randomized to intensive glycemic control versus standard of care utilizing the same protocol as the 2001 trial. Overall, there was no significant difference in in-hospital mortality (37.3% vs 40%, *P* = .33). Despite no overall mortality benefit, the incidence of mortality was lower in the subgroup of patients who stayed in the ICU for 3 or more days and received intensive glycemic control (43% vs 52.5%, *P* = .009). There was reduced morbidity in the intensive treatment group, including less newly acquired kidney injury, reduced duration of mechanical ventilation, shorter ICU stay, and shorter hospital stays. Despite some of the potential benefits of intensive glycemic control demonstrated in the Leuven studies, hypoglycemic episodes were increased with intensive glycemic control (5.2% vs 0.7% in the surgical ICU, 18.7% vs 3.1% in the medical ICU). Serious immediate side effects such as hemodynamic compromise and seizures were not reported. Hypoglycemia, however, was identified as an independent risk factor for death in the medical ICU population; this effect was not seen until at least 24

hours after the hypoglycemic episode. The reason for this result is unclear.

Two subsequent European randomized controlled trials failed to reproduce the results seen in the Leuven I study. Similar to the Leuven II study, the VISEP (Volume substitution and Insulin therapy in severe SEPsis) trial (n = 537) failed to demonstrate a mortality benefit with intensive glycemic control (80-110 mg/dL) compared to conventional insulin treatment (140-180 mg/dL). The study was stopped early due to the incidence of hypoglycemia (12.1% in the intensive group versus 2.1% in the conventional group, P < .001); however, 28-day mortality did not differ between groups at the conclusion of the study.

The Glucontrol study was a randomized control trial of intense versus intermediate glucose control in medicosurgical ICUs (n = 1,101). The trial was stopped early due to a high rate of unintended protocol violations. They only studied one-third of their intended number of patients, and the study was therefore underpowered. The intense control group had significantly more hypoglycemia, and no difference in ICU mortality was seen. Twenty out of 111 hypoglycemic events were attributed to inappropriate continuation of insulin infusion, seen more in the intense therapy group. Other trials over the years have tried to determine benefits of intense glucose control in specific patient populations with conflicting results. What is consistent, however, is the increase in hypoglycemic events with more intense therapy, making hypoglycemia the limiting factor in lower target glucose protocols.

Given the conflicting results of prior studies and known risks of hypoglycemia, the NICE-SUGAR study randomized critically ill patients expected to remain in the ICU for more than 3 days to intensive glucose control (81-108 mg/dL) versus conventional glucose control (≤180 mg/dL) in a multinational randomized trial. They found that severe hypoglycemia was more common in the intensive glucose control group (6.8% vs 0.5%; P < .001) and that 90-day all-cause mortality was increased (27.5% vs 24.9%; P = .02). The treatment effect did not differ significantly between surgical patients and medical patients. These authors concluded that a BG

target of 180 mg/dL or less resulted in lower morbidity and mortality compared to a more aggressive glucose target.

Several meta-analyses of intensive insulin therapy in critically ill patients have demonstrated increased occurrence of hypoglycemia in medical and surgical patients receiving intensive glycemic control; however, the variable results of the Leuven and NICE-SUGAR trials leave question as to the optimal BG target in an all-comer ICU population. These studies have several methodologic differences including variable BG targets, differences in BG measurement and nutritional support, and differences in patient population. A key methodologic difference between the Leuven, GLUCONTROL, and NICE-SUGAR trials is the BG targets utilized. The Leuven studies compared hyperglycemia (180-215 mg/dL) to intensive glycemic control, while the NICE-SUGAR and GLUCOTROL studies maintained intermediate targets in the conventional glycemic control arms (140-180 mg/dL). Furthermore, there were variable times spent at target BG, and methods for measuring BG differed. Patients in the NICE-SUGAR trial spent less than 50% of the time at target BG compared to 70% in the intervention arm of the Leuven studies. In the Leuven studies, BGs were measured strictly using blood gas analyzers on arterial blood, which provided increased accuracy compared to the variety of point-of-care (POC) glucose meters utilized in NICE-SUGAR. These inaccuracies could potentially lead to greater fluctuations in BG and delayed detection of hypoglycemia. Regarding nutrition, patients in the Leuven studies were more commonly given parenteral nutrition, which may increase risk of morbidity/mortality from bloodstream infection compared to mostly enteral nutrition in the NICE-SUGAR trial.

Surgical patients in Leuven I may have also had a shorter time to onset of stress-induced hyperglycemia than a possibly more chronically ill medical ICU population, meaning less stringent BG targets may be more reasonable in medical ICU patients. Given varying results in a variety of studies with different populations, differing BG targets have been suggested in select patient populations (Table 32.1). Beyond considerations for different ICU populations, it may be reasonable to consider a different target in

patients who maintained above-average BG concentrations before admission. This hypothesis is supported by a post hoc analysis of the Leuven studies demonstrating that the subgroup of patients with known diabetes did not benefit from intensive glycemic control. Furthermore, retrospective studies have associated tight glucose control in patients with higher A1Cs with increased risk of hypoglycemia and mortality.

TABLE 32.1 Considerations for Blood Glucose Targets in Select Populations

Population	Considerations
Cardiac surgery	• *Consider BG target <150 mg/dL.* • Majority of patient population in Leuven I (benefit with intensive glycemic control) • BG target <150 mg/dL demonstrated reduction in mortality, deep sternal wound infections, and hospital length of stay in a 17-y prospective study of ~5,000 patients.
Trauma	• *Consider moderate BG target (<150 mg/dL), maintain BG absolutely <180 mg/dL.* • Retrospective analysis of 2,028 patients with trauma at a level 1 trauma center found that intensive glycemic control (80-110 mg/dL) was associated with reduced mortality and hospital length of stay. • Retrospective analysis of 1,422 patients with trauma found that hyperglycemia (>189) was associated with increased mortality and that moderate glycemic control (80-140 mg/dL) was associated with the fewest hypoglycemic events.

Population	Considerations
Ischemic stroke, IPH, aneurysmal SAH, TBI	• *Consider moderate BG target (<150 mg/dL), maintain BG absolutely <180 mg/dL.* • Subgroup analysis from Leuven I study found that intensive glycemic control was associated with reduction in ICP, seizures, vasopressor use, and improved 1-y functional status. • Subgroup analysis from NICE-SUGAR found intensive glycemic control resulted in more hypoglycemic episodes, though these patients did not have increased mortality or adverse neurologic outcomes.

BG, blood glucose; ICP, intracranial pressure; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

Most recently, the CONTROLLING study investigated the impact of an individualized BG target based on preadmission hemoglobin A1C. Patients were randomized to conventional glycemic control (BG <180 mg/dL, n = 975) or individualized glycemic control (n = 942) in which the patients were maintained at their usual glycemia +15 mg/dL or less. The minimum glycemic target in the individualized glycemic control group was arbitrarily set to 111 mg/dL. Overall, the study did not demonstrate a difference in 90-day mortality, and the incidence of hypoglycemia (BG <72 mg/dL) was greater in the individualized glycemic control group (31.2% vs 15.8%, P < .0001). Notably, this study was underpowered; the mean A1C in both patients with and without diabetes was less than 7 mg/dL, and a nonvalidated web-based application developed by the study authors was used to guide insulin doses. Additional, prospective data are necessary to elucidate the risks and benefits of this type of personalized glycemic control in the critically ill.

Management

The conclusions and current recommendations based on these studies are still somewhat controversial. Table 32.2 lists the most

recent recommendations for glucose control in the ICU by the American Diabetes Association, American Heart Association, Society of Critical Care Medicine, and the American College of Endocrinology, which includes patients in all ICUs and hospital wards. The authors of the Surviving Sepsis Campaign advocate blood sugar goals of less than 180 mg/dL in critically ill patients in large part to limit hypoglycemia and to simplify management. Overall, some studies support intensive glucose control in patients who are expected to stay in the ICU for more than 3 to 5 days, those on corticosteroids, and select patient populations (Table 32.1). The postulated reason for benefit in longer ICU stays is that preventing hyperglycemia prevents its associated complications, which take time to develop. Based on these findings, it seems reasonable to exclude medical ICU patients who are eating and who are expected to be in the ICU for less than 3 days. However, it is not always possible to predict the length of ICU stays, and physician discretion is needed.

TABLE 32.2 Recommended Target Blood Glucose for Patients in the Intensive Care Unit

American Diabetes Association

- Initiate insulin starting at ≥180 mg/dL.
- Once insulin has started, a target glucose range of 140-180 mg/dL is recommended for most patients.
- More stringent targets may be appropriate for certain populations (110-140 mg/dL) providing a lower target does not confer increased hypoglycemic risk.

American College of Endocrinology
<180 mg/dL

American Heart Association
140-180 mg/dL (initiate therapy if >180 mg/dL)

Surviving Sepsis Campaign
<180 mg/dL

Society of Critical Care Medicine
<150 mg/dL in most patients, absolutely <180 mg/dL

While standard of care in the aforementioned studies (Leuven, NICE-SUGAR) is to prevent hyperglycemia in the critically ill, these studies do not provide sufficient evidence to support the use of subcutaneous insulin over IV insulin. Overall, there is no universally accepted method or regimen to maintain glycemic targets; however, continuous IV insulin infusions are preferred. Intermittently dosed short-acting subcutaneous insulin analogues can also be successfully used and may be a reasonable option. Of note, subcutaneous insulin should generally be avoided in patients who may have limited absorption of drugs from the subcutaneous tissue (shock, vasopressor use, hypothermia, peripheral edema/anasarca), patients who may have interruptions in nutrition for procedures, or patients with fluctuating clinical status. Longer-acting insulins are often avoided during early critical illness due to acute fluctuations in insulin requirements, and generally, all oral antihyperglycemic agents should be stopped.

The half-life of IV insulin is 5 to 9 minutes, which allows for rapid reversal of hypoglycemia when it occurs. Most ICUs now have standardized glucose algorithms, generally managed by nurses, which have shown to be valid ways to manage glucose. The most effective glucose algorithms are dynamic and incorporate the rate of glucose change into the insulin dose adjustments. Table 32.3 contains a validated insulin infusion protocol outlining how to initiate an insulin infusion, monitor BG, and manage hypoglycemia. Algorithm 32.1 and Tables 32.4 and 32.5 show how to manage the insulin infusion rate.

TABLE 32.3 Insulin Infusion Protocol

Initiating Insulin Infusion
Standard insulin infusion 100 U *regular human insulin* in 100 mL 0.9% normal saline
Preferred administration IV (*t*½ 5-9 min) via an infusion pump

Give initial bolus if BG >180 mg/dL.
Divide initial BG by 70 and round to nearest 0.5 U (eg, BG 250: 250/70 = 3.57, rounded to 4, so IV bolus 4 U).
After bolus, start infusion at same hourly rate as bolus (4 U/h IV in the earlier example).
If *BG <180 mg/dL*, divide by 70 for initial hourly rate with *NO bolus* (eg, BG 150 would be 150/70 = 2.15, rounded to 2, so start at 2 U/h IV).
Go to Algorithm 32.1 for instructions on changing the insulin infusion rate.
Blood Glucose Monitoring
Check BG q1h until stable (three consecutive values in target range).
Once stable, can change BG monitoring to q2h.
If stable q2h for 12-24 h, can change to q3-4h if no significant change in nutrition or clinical status.

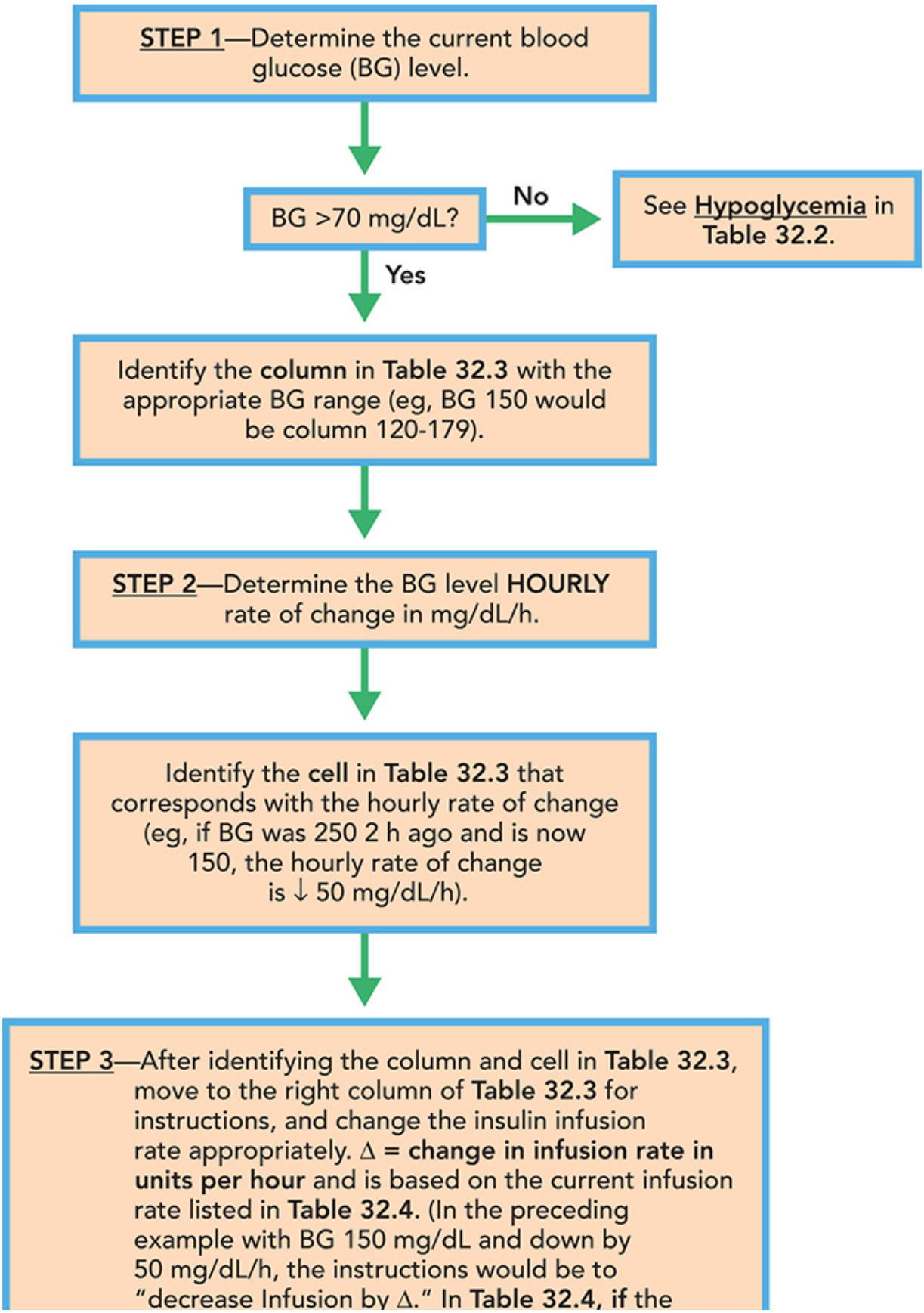
Resume q1h BG monitoring for BG >70 mg/dL with any of the following:
Change in insulin infusion rate
Initiation or cessation of corticosteroid or vasopressor therapy
Significant change in clinical status
Change in nutritional support (initiation, cessation, or rate change)
Initiation or cessation of hemodialysis or CVVHD
Hypoglycemia (BG <70 mg/dL)
If *BG <50 mg/dL*, stop infusion and give 25 g dextrose 50% (1 amp D50) IV.
Recheck BG q10-15min.
When BG >90 mg/dL, recheck in 1 h. If still >90 mg/dL after 1 h, resume insulin infusion at *50% most recent rate.*
If *BG 50-69 mg/dL*, stop infusion.
If symptomatic or unable to assess, give 25 g dextrose 50% (1 amp D50) IV.
Recheck BG q15min.[a]
If asymptomatic, consider 12.5 g dextrose 50% (1/2 amp D50) or 8 oz. fruit juice po.
Recheck q15-30min.[a]

BG, blood glucose; CVVHD, continuous venovenous hemodialysis; IV, intravenous; PO, by mouth.

[a]When, BG >90 mg/dL, recheck in 1 h. If still >90 mg/dL after 1 h, resume insulin infusion at 75% most recent rate.

Modified from Goldberg PA, Siegel MD, Sherwin RS, et al. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care.* 2004;27(2):461-467, with permission.

ALGORITHM 32.1 Changing the Insulin Infusion Rate


STEP 1—Determine the current blood glucose (BG) level.
BG >70 mg/dL?
No
See Hypoglycemia in Table 32.2.
Yes
Identify the column in Table 32.3 with the appropriate BG range (eg, BG 150 would be column 120-179).
STEP 2—Determine the BG level HOURLY rate of change in mg/dL/h.
Identify the cell in Table 32.3 that corresponds with the hourly rate of change (eg, if BG was 250 2 h ago and is now 150, the hourly rate of change is ↓ 50 mg/dL/h).
STEP 3—After identifying the column and cell in Table 32.3, move to the right column of Table 32.3 for instructions, and change the insulin infusion rate appropriately. Δ = change in infusion rate in units per hour and is based on the current infusion rate listed in Table 32.4. (In the preceding example with BG 150 mg/dL and down by 50 mg/dL/h, the instructions would be to "decrease Infusion by Δ." In Table 32.4, if the

current infusion rate was 5 U/h, you would decrease the infusion by 1 U/h.)

TABLE 32.4 Current Blood Glucose Level and Rate of Change

BG 70-89 mg/dL	BG 90-119 mg/dL	BG 120-179 mg/dL	BG >180 mg/dL	Instructions
		BG ↑ by >40 mg/dL/h	BG ↑	*Increase infusion* by 2D
	BG ↑ by >20 mg/dL/h	BG ↑ by 1-40 mg/dL/h *or* *BG unchanged*	*BG unchanged OR* BG ↓ by 1-40 mg/dL/h	*Increase infusion* by D
BG ↑	BG ↑ by 1-20 mg/dL/h, *BG unchanged, or* BG ↓ by 1-20 mg/dL/h	BG ↓ by 1-40 mg/dL/h	BG ↓ by 41-80 mg/dL/h	*No infusion change*
BG unchanged or BG ↓ by 1-20 mg/dL/h	BG ↓ by 21-40 mg/dL/h	BG ↓ by 41-80 mg/dL/h	BG ↓ by 81-120 mg/dL/h	*Decrease infusion* by D
BG ↓ by >20 mg/dL/h[a]	BG ↓ by >40 mg/dL/h	BG ↓ by >80 mg/dL/h	BG ↓ by >120 mg/dL/h	*Hold infusion* × 30 *min then decrease by 2D*

See Algorithm 32.1 for instructions.

BG, blood glucose; D, insulin infusion rate.

[a]Hold insulin infusion; check BG q15-30min; when >90 mg/dL, restart infusion at 75% most recent rate.

TABLE 32.5 Changes in Insulin Infusion Rate (*D*) in Units per Hour

Current Infusion Rate (U/h)	*D* = Rate Change (U/h)	2*D* = 2 × Rate Change (U/h)
<3	0.5	1
3-6	1	2
6.5-9.5	1.5	3
10-14.5	2	4
15-19.5	3[a]	6[a]
20-24.5[a]	4[a]	8[a]
>25[a]	5[a]	10[a]

[a]Infusions typically range from 2 to 10 U/h. Doses in excess of 20 U/h are unusual and a physician should be notified to explore potential contributing factors such as errors in insulin dilution and administration.

In managing glucose, insulin infusion adjustments must be made based on changes in carbohydrate intake. For example, a change in the dextrose 5% rate from 150 mL/h (180 g carbohydrates normalized during a 24-hour period) to 75 mL/h (90 g carbohydrates normalized during a 24-hour period) will require a decrease in the insulin infusion rate to prevent hypoglycemia. In critically ill patients, multiple sources of carbohydrates need to be taken into consideration when calculating the insulin dose such as parenteral nutrition, enteral tube feeds, and glucose-containing IV fluid. Nutrition, whether enteral or parenteral, should be given as a continuous infusion rather than intermittent boluses to prevent significant fluctuations in BG. It is often critical to reassess caloric intake every 12 to 24 hours. The patients most at risk for hypoglycemia are those with renal failure and hepatic failure. Close

attention to detail and less aggressive upward titration schedules in patients with liver and renal failure should allow insulin drips to be safely used. Meticulous attention must also be paid to patients with impaired mental status who are unable to perceive and respond to low glucose levels.

The implementation of any protocol, whether taken from the literature or developed locally, especially one as complex as an IV insulin drip protocol, requires a significant amount of education and training. Even under controlled conditions, the protocol is susceptible to frequent violations, as seen in the Glucontrol study. The violations could be as simple as missed BG levels or as serious as a failure to adjust the insulin infusion rate. Human error must be taken into consideration when evaluating BG control.

Computerized calculation of the drip rate has been shown to minimize mistakes and may improve outcomes. Our institution has studied EndoTool in patients undergoing elective cardiac surgery, requiring cardiopulmonary bypass, and compared glycemic control to a paper-based protocol using a target of 100 to 150 mg/dL. The computerized protocol resulted in a higher proportion of patients achieving the desired target for longer time and quicker than the paper-based protocol with no significant difference in hypoglycemia. (Other computerized-based protocols include enhanced model predictive control [eMPC] [*BMC Anesthesiol.* 2016;16:8.], Glucocare IGC system [*Diabetes Technol Ther.* 2013;15(3):246-252.], and Glucommander.)

Once patients improve and are ready to be discharged from the ICU, IV insulin needs to be switched to subcutaneous insulin. Using an sliding scale short-acting insulin alone results in rebound hyperglycemia. The development of diabetic ketoacidosis and hyperglycemic hyperosmolar state in the hospital is considered “never events” by Centers for Medicare and Medicaid Services (CMS). Using basal long-acting insulin (neutral protamine Hagedorn [NPH], glargine, or detemir) combined with prandial and sliding scale short-acting insulin (aspart, lispro, glulisine) will lead to better glycemic control. When calculating the dosage, consideration needs to be made for the patient’s prior history of diabetes, type of

diabetes, stress level, prior insulin dosage, steroid use, and general clinical status. There are no consensus guidelines on how to effectively transition from IV to subcutaneous insulin; however, retrospective data suggest a transition to 50% to 80% of their 24-hour IV insulin requirements is safe and effective. The 24-hour IV insulin requirement is typically calculated by averaging the hourly insulin infusion rate in the 6 hours before transition. This dose can then be evenly divided into basal and prandial insulin. Long-acting insulin needs to overlap with discontinuation of the drip (generally by 1-2 hours) to prevent rebound hyperglycemia.

Attention should be paid to what glucose analyzer is used (blood gas, core laboratory, POC glucose oxidase, or POC glucose dehydrogenase), the source of patient sample (arterial, capillary, central venous), the conditions the patient presents with (anemia, hypoxia, poor peripheral perfusion), and medications they are receiving (acetaminophen, oxygen, vasopressors, mannitol, ascorbic acid, intravenous immunoglobulin (IVIG), peritoneal dialysis) that cause changes in glucose results.

Anemia (hematocrit [Hct] <34%) has been shown to cause significant error, overestimating glucose with some POC glucometers. Dosing insulin based on falsely elevated glucose values could contribute to hypoglycemia in intensively treated patients in ICU settings. The use of formulas correcting for the level of anemia has been shown to reduce hypoglycemic events in ICU patients and has been incorporated into most meters commonly in use in the hospital setting. Meters using glucose dehydrogenase strips are affected by maltose in IVIG and icodextrin from peritoneal dialysis, and therefore should not be used in health care facilities until these problems are corrected.

The Food and Drug Administration (FDA) has issued an off-label designation for POC glucose meters not approved for their use in critically ill patients. However, the FDA did not define critical illness, which has allowed institutional discretion of choice of meter. To date, two POC glucose meters that automatically correct for Hct, hypoxia, and interfering reducing substances have been approved by the FDA to be used in these vulnerable population (Nova StatStrip and Nova

StatStrip Xpress Systems). By the end of 2015, approximately 50% of the hospitals in the United States reported using them. Off-label use of other meters can result in regulatory burden with mandatory training and certification of the staff.

Even without an identified clinical interference, glucose meters can have an error margin of up to 20%, whereas laboratory analyzers must be below 10% to meet FDA standards. Arterial blood measured by POC glucometers is more accurate than capillary glucose and should be used when available in ICU patients on IV insulin. A “stat” blood sample should be sent to the laboratory when in doubt of the glucose reading or for values higher than the detectable range on the device.

As the use of continuous glucose monitors (CGMs) expands, investigation into their utility in the critically ill population continues. Multiple randomized clinical trials have evaluated the impact of CGMs on glycemic control, the risk of hypoglycemia, and the associated nursing workload in critically ill patients. Holziger et al randomized 124 patients on mechanical ventilation to real-time (RT) CGM with glucose values given every 5 minutes (n = 63) versus a control group (n = 61) to target normoglycemia (BG 80-100 mg/dL). Mean glucose level was not improved using CGM, but the risk of severe hypoglycemia was reduced (1.6% vs 11.7%, P = .031) with an absolute risk reduction of 9.9% and a number to treatment of 10.1. A subsequent study by De Block et al studied 35 patients in the medical ICU that were randomized to RT-CGM (n = 16) or blinded CGM with a normoglycemic target of 80 to 100 mg/dL using a modified version of the Yale infusion protocol for a median time of 96 hours. CGM data were only used to obtain additional arterial blood samples if the rate of change in glucose exceeded 25 mg/dL per 30 minutes. Glucose variability and time spent at target glycemia and hypoglycemia were similar between groups. Because the insulin infusion protocol provided very good control, CGM use did not improve glucose control or reduce hypoglycemia. Similarly, a study conducted by Boom et al (n = 156) randomizing patients to CGM-guided glucose management or POC glucose checks did not find a difference in glycemic control between groups; however, did note a

significant reduction in daily nursing workload between groups. While most available data seem to suggest CGMs may be a reliable and appealing option in the critically ill population, FDA-approved devices in this population are lacking. Continued investigation is warranted to determine the potential role of these devices in the ICU.

In summary, although the current recommendations for glucose targets are widespread, evidence supporting the goal of less than 180 mg/dL is still lacking. Treating hyperglycemia in critically ill patients can lead to decreased morbidity and mortality. Available data suggest medical and postsurgical patients who are in the ICU for more than 3 to 5 days are most likely to benefit from a lower target range, but mortality benefit is lessened or eliminated when hypoglycemic events increase. Insulin in critically ill patients should generally be given intravenously to allow rapid reversal of hypoglycemia if it occurs, with early data suggesting that critically ill medical and cardiac patients may be most sensitive to the effects of hypoglycemia. Insulin infusion protocols implemented by well-trained staff can be effective ways to manage BG. Paying careful attention to changes in patients' clinical condition and nutritional status, as well as vigorous glycemic monitoring by hospital staff, will minimize hypoglycemic events. Standardizing the glucose monitoring methods and using more accurate technologies may reduce hypoglycemic events and allow for safer intense glucose management, resulting in better outcomes in future trials.

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SECTION VII Oncologic Emergencies

33 Oncologic Emergencies

Samuel Windham and Colleen McEvoy

Oncologic emergencies are complications of cancer that require immediate recognition and treatment due to the high risk of severe morbidity and/or mortality. As the prevalence of cancer increases, the number of patients with oncologic conditions admitted to the intensive care unit (ICU) will continue to grow; currently, 20% of patients admitted to the ICU will have a cancer diagnosis. The management of patients with oncologic conditions also requires a multidisciplinary approach with close collaboration with oncologists to provide optimal care.

In this chapter, we will focus on the pathophysiology, diagnosis, and management of malignant spinal cord compression, superior vena cava syndrome, hyperleukocytosis, and leukostasis, as well as tumor lysis syndrome (TLS) and acute graft-versus-host disease. We will also discuss novel immune effector cell–related complications, including cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Other possible oncologic emergencies, such as cardiac tamponade, adrenal insufficiency, pulmonary embolism, urinary or bowel obstruction, and febrile neutropenia, are discussed in other chapters.

Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) is a relatively common complication that can result in devastating consequences, such as irreversible loss of neurologic function, if not promptly recognized and treated. Spinal lesions occur in 50% of patients with osseous metastasis, and MSCC develops in 5% to 10% of those patients. MSCC is thought to develop through either hematogenous spread to

the vertebrae or soft tissue extension from lytic or sclerotic lesions in hematologic malignancies. The resulting mass causes symptoms by compressing the epidural venous plexus, spinal artery, thecal sac, and spinal cord. Further weakening of bone can cause vertebral compression fractures, resulting in bony fragments with direct damage to the spinal cord. Metastatic solid malignancies of the lung, breast, and prostate are most commonly associated with MSCC, while non-Hodgkin lymphoma, multiple myeloma, rectal cancer, and sarcomas are less common causes. MSCC may present initially in 20% of patients with undiagnosed malignancy.

Any patient with cancer presenting with new-onset pain, sensory deficits, weakness, or dysfunction of bowel or bladder should have significant concern for MSCC. Early recognition is essential, as restoration of neurologic function and prognosis are directly related to the degree of initial neurologic damage. Pain is the most common presenting symptom (~90%). Frequently, pain distribution is based on the location of compression, with mid-scapular pain in cervical lesions, band-like chest or abdominal pain in thoracic lesions, and hip or lumbosacral pain in lumbosacral lesions. Pain is typically described as localized or radicular. MSCC occurs more often in the thoracic spine than in the lumbosacral or cervical spine. This pain is usually exacerbated by movement, especially coughing or sneezing, as well as lying flat. Paresthesias and sensory deficits are also possible in affected dermatomes, occurring in 70% of cases, but usually go unrecognized by patients. Motor deficits are highly variable and may include anything from subtle clumsiness or feelings of heaviness to weakness with an inability to ambulate to paralysis. Lower motor neuron involvement tends to present as asymmetric weakness and hyperreflexia that starts distally, with hyporeflexia at the point of the lesion. Spinal shock with hyporeflexia and flaccid paralysis below the lesion is also possible. The presence of autonomic deficits like bowel or bladder dysfunction tends to occur later in the course and portends a poorer outcome after treatment.

MSCC requires a high index of suspicion in any patient with metastatic disease and back pain. Patients with possible MSCC should undergo a thorough history and physical examination, with

attention to new pain or neurologic deficits. Urinary retention should be investigated by obtaining post-void residual bladder volume or examination with ultrasound, and anal sphincter function requires a digital rectal examination. The most important test for MSCC is imaging, with magnetic resonance imaging (MRI) being the modality of choice. The entire spine should be imaged, as one in four patients will have noncontiguous levels of compression. Also, symptomology can poorly predict the level of the lesion, and treatment planning benefits from a complete image. Computed tomography (CT) myelography should only be obtained if MRI is contraindicated, as it may have lower diagnostic accuracy. Other imaging modalities, such as x-ray and positron emission tomography (PET), may miss soft tissue components. Angiography can be used for hypervascular tumors (ie, sarcoma, thyroid, melanoma, renal cancer). Tissue biopsy of either the MSCC lesion or an easier-to-approach lesion should be pursued, as it affects treatment decisions.

Early diagnosis and treatment are essential since neurologic prognosis depends on motor function at the time of diagnosis. Prompt empiric treatment with steroids is the first line of treatment if MSCC is suspected. Steroids provide analgesia and potentially preserve neurologic function by decreasing spinal cord edema if administered promptly. Steroids can also reduce tumor burden in some cases, such as lymphoma. Steroids should be administered prior to radiotherapy. A common regimen is dexamethasone 10 mg IV or PO followed by 4 mg IV or PO every 6 hours. This can be continued through the acute treatment period followed by a taper.

All patients should be evaluated by radiation oncology, spinal surgery, and medical oncology. Extremely acute presentations of pain and neurologic deficits could indicate vertebral burst fractures and require urgent surgical intervention. Surgical decompression is indicated where there is significant cord compression, medically intractable pain, radioresistant tumors, evidence of spinal instability, and when symptoms progress while receiving radiotherapy. Radiotherapy is recommended for those with known tumor sensitivity to X-ray telescope (XRT), unable to tolerate surgery, shorter life expectancy, in diffuse spinal disease, or symptoms for greater than

48 hours. Some types of malignancy, like sarcomas, are considered radioresistant and may not benefit from radiation therapy (XRT). Patients should also be evaluated for vertebral instability following XRT, depending on the extent of the disease. Prognosis is poor, and survival after the diagnosis of MSCC is 3 to 6 months. Inpatient mortality ranges from 7.7% to 11.5%, emphasizing the need for early recognition and treatment.

Superior Vena Cava Syndrome

Malignant superior vena cava syndrome (SVC) is the obstruction of the superior vena cava, resulting in decreased blood return to the right atrium. It can occur secondary to various malignancies, including non–small cell lung cancer (50% of cases), small cell lung cancer (25%), non-Hodgkin lymphoma (10%), metastatic disease to lymph nodes (10%), thymoma, and germ cell tumors. Due to prevalent use of intravascular devices, the incidence of thrombotic causes of SVC syndrome is increasing.

SVC syndrome can be caused by (1) extrinsic compression from a tumor or bulky lymphadenopathy, (2) tumor invasion into the SVC itself, (3) or venous thrombosis due to malignancy and indwelling catheters. Blood vessels proximal to the occlusion become dilated, which leads to symptomatology from impaired venous drainage. Collateral vessels develop to reestablish blood flow to the right atrium. Collateralization takes time to develop, so more rapidly developing SVC obstruction can lead to more severe symptoms as collateral flow has not yet been established.

SVC syndrome can be the initial presentation of malignancy. Symptoms are related to increased venous pressure in the upper body due to the obstruction. Common findings include facial swelling, upper extremity edema, distended neck or chest veins, facial plethora, cough, dyspnea, and syncope. Life-threatening cerebral, laryngeal, and pharyngeal edema can develop, with cerebral edema presenting as altered mental status, headaches, and vision changes. Fatal brainstem herniation can occur if not treated.

Airway edema can result in stridor, hoarseness, dysphagia, cough, and possible airway compromise requiring intubation. Hemodynamic compromise can occur due to decreased venous return to the heart.

Diagnostic work-up should include imaging with CT with contrast to identify the cause of the obstruction and the presence of thrombosis. CT imaging may potentially aid in diagnosing malignancy via tissue biopsy and help guide therapy. MRI is an option to determine the location of obstruction and the presence of collaterals. Venography may be needed if endovascular stenting or surgery is planned.

Treatment of SVC syndrome depends on acuity, severity of symptoms, and underlying malignancy/etiology. The focus of management is the identification of any life-threatening symptoms, including cerebral edema, laryngeal edema, and hemodynamic instability. Such patients require urgent stabilization and venogram with possible endovascular stenting with or without catheter-directed thrombolysis.

In the absence of life-threatening symptoms, a multidisciplinary approach to treatment options, such as XRT and systemic chemotherapy, is warranted, as treatment of the underlying malignancy is key to management. While awaiting a tissue diagnosis and definitive treatment plan, endovascular stenting has been shown to be safe and effective. It can improve symptoms within the first 24 to 72 hours. However, complications such as stent migration, stenosis, pericardial tamponade, and pulmonary embolism have been seen in less than 10% of cases. Depending on the underlying cancer type, XRT and systemic chemotherapy can result in rapid regression of symptoms. Anticoagulation may be considered a treatment for SVC syndrome due to thrombosis; however, current data suggest it may not improve outcomes, necessitating an assessment of bleeding risk before starting anticoagulation. Patients with malignant SVC syndrome have a life expectancy of less than 9 months, varying depending on the type of malignancy.

Hyperleukocytosis and Leukostasis

Hyperleukocytosis (white blood cell [WBC] counts >50,000 to 100,000) is considered a medical emergency and can be seen in both acute and chronic leukemias. As many as one in five patients with acute myeloid leukemia (AML) present with hyperleukocytosis. Hyperleukocytosis can result in life-threatening conditions such as leukostasis, TLS, and disseminated intravascular coagulation (DIC). Leukostasis is a clinical syndrome associated with high numbers of circulating immature leukocytes, called “blasts.” While leukostasis typically occurs at higher WBC counts (>100,000/mm^3), it can be seen at levels as low as WBC 50,000/mm^3; so clinical suspicion must remain high in patients at risk. The mechanism of disease is incompletely understood but likely involves increased impaired microvascular flow with hypoperfusion to the lungs, heart, and brain due to increased blood viscosity, increased utilization of metabolites and cytokines by active blasts, and inflammation from extravasated cells causing endovascular damage. Chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML) have a higher risk of hyperleukocytosis (20%-50%) than AML (5%-15%) and acute lymphoblastic leukemia (ALL) (10%-25%). Mortality related to end-organ dysfunction from leukostasis is particularly high in AML, especially in the first 24 hours and the first week. Leukostasis can be difficult to diagnose, since clinical presentation and imaging findings of leukostasis are similar to infectious and hemorrhagic complications seen in patients with leukemias.

Symptoms are most commonly related to respiratory and central nervous system (CNS) dysfunction, including shortness of breath, hemoptysis, and acute hypoxemic respiratory failure requiring mechanical ventilation. CNS dysfunction can present with confusion, altered mental status, changes in vision, focal deficits, and seizures. Other manifestations include myocardial infarction, pulmonary embolism, priapism, retinopathy, papilledema, appendicitis, and acute kidney injury. The presence of respiratory and CNS manifestations portend a worse prognosis with mortality as high as

90%. Chest imaging can show diffuse alveolar infiltrates, and brain imaging may reveal ischemia, hemorrhage, or even masses. Laboratories may reveal hypokalemia, pseudohyperkalemia due to cell death in vitro, or true hyperkalemia. Other signs of TLS, as discussed later, can be present. Falsely low Pa_{O_2} levels are possible due to the so-called "leukocyte larceny syndrome." Thrombocytopenia can be present despite reassuring laboratory value, as some automatic cell counters read that abnormal WBCs as platelets. Given the clinical nature of the diagnosis, any patient at risk of leukostasis should be evaluated for end-organ damage.

Treatment goals include cytoreduction with leukapheresis, hydrea, and treatment of the underlying malignancy with chemotherapy. Close collaboration with oncology is vital to management, as chemotherapy aimed at reducing peripheral and marrow blast counts should be started as soon as possible. Hydroxyurea is used in all patients with hyperleukocytosis. Leukopheresis is considered for symptomatic patients and those with blast counts more than 50,000 mm^3 in AML and more than 250,000/mm^3 in ALL. One session of leukapheresis can decrease the count by 25% to 50%, but a rebound effect may occur after stopping due to migration from the bone marrow, highlighting its use as a bridge to chemotherapy. However, the timing, number of pheresis session, and target WBC are not well defined. Blood transfusions are typically restricted, tolerating lower levels of anemia than usual, to avoid further worsening of symptoms. TLS and DIC should be monitored for and treated if identified. Finally, any suspicion of infection should be investigated with appropriate cultures, and antibiotics started while awaiting results.

Tumor Lysis Syndrome

TLS is a common oncologic emergency, where sequelae can become life-threatening if not recognized and treated promptly. TLS is a clinical consequence of the sudden release of potassium,

phosphate, and uric acid from purine metabolism within malignant cells undergoing cell death. Hyperkalemia is usually the earliest and most severe manifestation. Phosphate binds calcium, which then precipitates in the renal tubules along with uric acid, resulting in kidney injury and possibly failure, as well as clinically significant hypocalcemia. Renal dysfunction can decrease removal of phosphate and uric acid, leading to worsening metabolic abnormalities. The overall incidence of TLS varies based on malignancy type, with the highest incidence observed in those with hyperleukocytosis (ie, acute leukemias), high tumor burden, or rapid response to chemotherapy (ie, CLL and small cell lung cancer). Hematologic malignancies (HM) have the highest rate (up to ~40% in some patients) and can occur spontaneously. Patients with renal insufficiency prior to chemotherapy are also at increased risk. Acute renal failure induced by TLS is usually reversible, even if hemodialysis is required, which occurs in approximately one out of six patients. Patients are characterized into low, intermediate, and high risk based on the type of malignancy, laboratory data, and history of renal insufficiency.

Clinical manifestations of TLS are secondary to the metabolic derangements and include cardiac arrhythmias, mental status changes, stupor, renal failure, tetany, and cardiac arrest. Any patient at risk for TLS requires frequent monitoring of electrolytes, lactate dehydrogenase, and uric acid levels, particularly those diagnosed with acute leukemia or at the time of initiation of chemotherapy. Management of at-risk patients focuses on prevention. Pretreatment with aggressive IV hydration is started to avoid prerenal kidney injury in high-risk patients. Diuretics may be given to maintain urine output (goal >100 mL/h) and increase potassium excretion. Urine alkalization has not been demonstrated to be more effective than volume expansion alone and may promote calcium phosphate deposition in organs. Therefore, it is not recommend. Allopurinol is a xanthine oxidase inhibitor that blocks uric acid production. Allopurinol should be given to those at intermediate and high risk of TLS as prophylaxis prior to initiation of chemotherapy. Dosing is 300 to 600 mg/d divided into three doses, with dose reduction for renal

dysfunction. Rasburicase is a recombinant urate oxidase that breaks down uric acid that has already formed into metabolites. Rasburicase has been shown to be safe and effective at lowering uric acid levels but is limited to severe cases of TLS. Of note, rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and has associated side effects of anaphylaxis and methemoglobinemia. There are multiple guidelines for management of TLS, but no studies have compared outcomes; however, early recognition and aggressive treatment are emphasized by all.

Cytokine Release Syndrome and Immune Effector Cell–Associated Neurotoxicity Syndrome

CRS and ICANS are potentially life-threatening toxicities associated with the administration of novel immunotherapies, including bispecific antibodies (ie, blinatumomab), immune effector cell (IEC) therapies such chimeric antigen receptor–T cells (CAR-T) therapy, T-cell receptors (TCRs) therapy, as well as haploidentical hematopoietic stem cell transplant. The main focus of this discussion will be on the revolutionary CAR-T therapy, as more than 30% to 40% of patients receiving CAR-T therapy require ICU admission. CAR-T therapy are used to treat various hematologic malignancies where T cells are taken from the patient or donor blood, modifying them to target tumoral antigens specific to the malignancy, such as CD19 in B-cell cancers, and then readministered to the patient to treat the underlying malignancy. Toxicities, including CRS and ICANS, are related to an exaggerated inflammatory response caused by the activation or engagement of endogenous or infused T cells and/or other IEC, which can progress to vasodilatory shock, hypoxemic respiratory failure, multiorgan failure, and neurotoxicity.

CRS is the most common toxicity, seen in 60% to 90% patients receiving CAR-T therapy. The prevalence is dependent on the cell

construct and type of malignancy. Incidence and severity increase with a large tumor burden and higher infusional cell dose, with 15% to 30% of patients experiencing more than grade 3 and about 20% require vasopressors. The “supraphysiologic” inflammatory response is associated with marked elevations in cytokines (eg, IL-6, IL-8, IL-10, TNF-alpha, INF-gamma), leading to many clinical manifestations. Activation markers like Ang-2 and von Willebrand factor, intercellular adhesion molecules, have also been implicated in the development of capillary leak, hypotension, and coagulopathy. C-reactive protein (CRP) and ferritin levels are used as biomarkers as increased levels correlate with severity of CRS. Hallmark manifestations include fever, hypoxemia, and hypotension. The American Society for Transplantation and Cellular Therapy developed a grading based on these hallmark manifestations (Tables 33.1 to 33.3). As the syndrome advances, multiorgan dysfunction, including respiratory, cardiac, renal, hepatotoxicity, skin lesions, and DIC, may occur. Acute hypoxemic respiratory failure can progress from noncardiogenic pulmonary edema to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Cardiac toxicity can manifest as arrhythmias, heart block, hypotension, and shock. CRS usually presents within 1 to 7 days post–CAR-T infusion but can occur as late as 10 weeks after infusion. The mainstays of treatment are the monoclonal anti-IL-6 antibody tocilizumab and corticosteroids. Anakinra, an interleukin-1 receptor antagonist, has also been used for refractory or persistent CRS and/or ICANS. Treatment is based on grading; however, there is no consensus on management and remains institution-specific.

TABLE 33.1 Cytokine Release Syndrome (CRS) Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38.0 °C	Temperature ≥38.0 °C	Temperature ≥38.0 °C	Temperature ≥38.0 °C

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, facemask, nonrebreather, or Venturi mask	Requiring positive pressure (CPAP, BiPAP, IMV)

BiPAP, biphasic positive airway pressure; CPAP, continuous positive airway pressure; IMV, invasive mechanical ventilation.

TABLE 33.2 Immune Effector Cell–Associated Encephalopathy (ICE) Score

Orientation: orientation to year, month, city, hospital, 4 points
Naming: naming three objects (eg, point to clock, pen, button): 3 points
Following commands: (eg, show me two fingers or close your eyes and stick out your tongue): 1 point
Writing: able to write a standard sentence (eg, Our national bird is the bald eagle): 1 point
Attention: count backward from 100 by 10: 1 point

TABLE 33.3 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (unarousable and unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly, or nonconvulsive seizures detected on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min), or repetitive clinical or electrical seizures without a return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging: decerebrate or decorticate posturing; or CN VI palsy; or papilledema; or Cushing triad

EEG, electroencephalogram; ICE, immune effector cell–associated encephalopathy; ICP, intracranial pressure; IMV, invasive mechanical ventilation. Derived from Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

ICANS is a clinical and neuropsychiatric syndrome that can occur after CAR-T therapy in 70% to 80% of patients, with 30% to 40% of cases being severe. Neurotoxicity presentations can vary significantly but can be considered in three main categories: (1) acute presentation typically occurs 7 days after infusion with or without concurrent CRS; (2) delayed-within days to weeks following CRS; (3) cerebral edema is a rare complication but can be sudden and lethal. The syndrome is usually reversible but can take days to weeks to resolve. A grading system has been developed and includes assessment of immune effector cell–associated encephalopathy (ICE) assessment tool, level of consciousness, presence of seizure, and degree of motor findings (see Figure 33.1). Pathophysiology is similar to CRS, and studies have shown endothelial dysfunction of blood-brain barrier and trafficking of CARs into the CNS. Most patients will be placed on prophylactic antiepileptics. Monitoring for and management of seizures, status epilepticus, and cerebral edema are essential. High-dose

corticosteroids are used to reverse symptoms. Anakinra is also being used at many centers to treat ICANS. Tocilizumab is indicated for concurrent CRS but not for ICANS alone.

It is essential for intensivists to be familiar with the presentation and management of these conditions given the unique features of the complications in the oncology patient population. Close collaboration with oncology and critical care teams is vital to providing optimal care to patient.

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SECTION VIII

TEMPERATURE AND ENVIRONMENTAL REGULATION

34 Temperature Alterations

Matthew Abbott and Derek E. Byers

Temperature Regulation

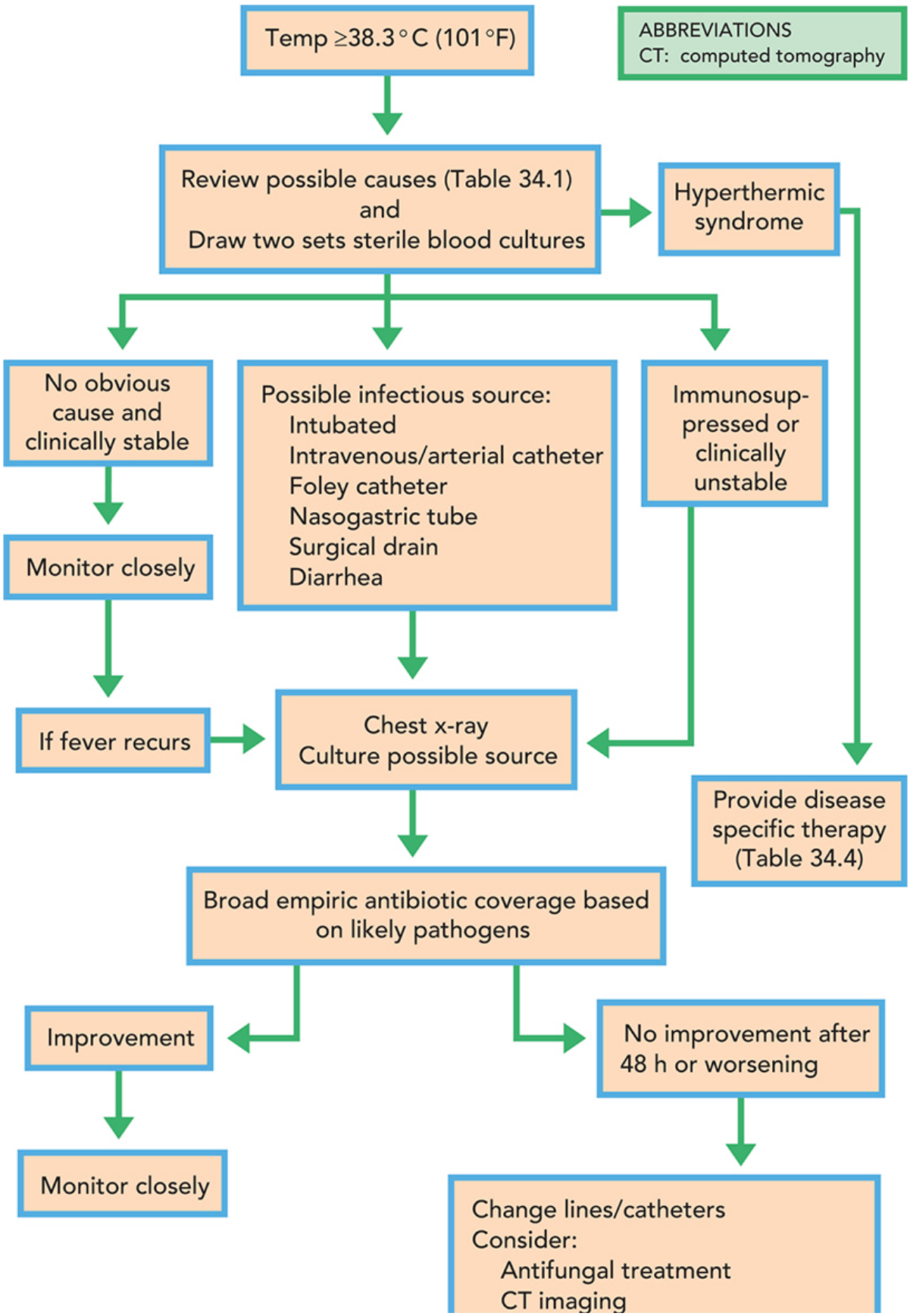
Temperature regulation involves a balance between heat production and dissipation. Basic metabolic processes generate heat, and various adaptive processes ranging from vasodilation and sweating to vasoconstriction and shivering help maintain the normal core body temperature at 37 °C (98.6 °F). Core body temperature varies by approximately 0.5 to 1.0 °C as a result of diurnal variation. Maintenance of euthermia is controlled by the hypothalamus, the brainstem's serotonergic system, and cellular mitochondrial oxidative phosphorylation. Interruption or alterations in any of these processes can lead to temperature dysregulation.

Fever and Hyperthermia

Fever is a preserved evolutionary response to infection and other physiologic stressors. Adjustment in the hypothalamic temperature set point results in an increase in body temperature. Studies have shown that immune activity is augmented at elevated temperatures. Blocking the body's normal physiologic increase in body temperature by forced cooling or antipyretic therapy may prolong the duration of infectious symptoms. However, fever increases metabolic demand and oxygen consumption, which may be detrimental, and is often associated with worse outcomes in the setting of neurologic injuries. Abnormally high fevers (prolonged >103 °F/39.4 °C, or any fever >105 °F/40.5 °C) can have undesired consequences, including seizures, disseminated intravascular coagulation, renal failure, and death.

A task force including societies in critical care medicine and infectious disease defines *fever* as a temperature of 38.3 °C or more (≥101 °F) measured from a reliable site (oral, esophageal, rectal, auditory, intravenous, or bladder thermistor). Temperatures above 38.3 °C warrant a thorough history and physical examination to determine whether infection is the cause. The initial workup should include, at a minimum, two sets of blood cultures drawn from two different sterile sites, chest radiograph (especially for intubated patients), and urinalysis with microscopy. Additional cultures and testing should be ordered as indicated. See Algorithm 34.1 for more information. The decision to begin antibiotic therapy is based on the patient's clinical stability, likelihood of infection, and immune status. Empiric broad-spectrum antimicrobial therapy should be started for immunocompromised patients or those with sepsis while awaiting further workup (see Chapter 43, Infections in the Immunocompromised Host). Stable patients without an obvious infectious source may be monitored closely for fever recurrence and culture results before initiating therapy.

ALGORITHM 34.1 **Workup for Fever/Hyperthermia**


Temp ≥38.3 °C (101 °F)
ABBREVIATIONS
CT: computed tomography
Review possible causes (Table 34.1)
and
Draw two sets sterile blood cultures
Hyperthermic syndrome
No obvious cause and clinically stable
Possible infectious source:
Intubated
Intravenous/arterial catheter
Foley catheter
Nasogastric tube
Surgical drain
Diarrhea
Immunosup-pressed or clinically unstable
Monitor closely
If fever recurs
Chest x-ray
Culture possible source
Provide disease specific therapy (Table 34.4)
Broad empiric antibiotic coverage based on likely pathogens
Improvement
No improvement after 48 h or worsening
Monitor closely
Change lines/catheters
Consider:
Antifungal treatment
CT imaging

Venous dopplers
Noninfectious cause (Table 34.1)

Table 34.1 lists infectious and noninfectious causes of fever and hyperthermia in the intensive care unit (ICU). Most fevers are the result of infection, and appropriate antibiotic therapy should lead to improvement within a few days. However, a temperature of 38.3 °C or more (≥101 °F) can also occur in the absence of infection. Awareness of these causes can help avoid unnecessary antibiotics, diagnostic testing, and loss of time. Temperatures above 38.9 °C (>102 °F) are uncommon for noninfectious causes, with the exception of hyperthermia, drugs, transfusion reactions, and hematologic malignancies.

TABLE 34.1 Causes of Fever and Hyperthermia

Infectious causes

- Ventilator-associated pneumonia
- *Clostridioides difficile* colitis
- Intravenous catheter infection
- Urinary tract infection
- Nosocomial pathogen (gram-negative bacteria, *Candida* species)
- Sinusitis
- Abscess formation
- Central nervous system infection (meningitis, VP shunt)
- Wound infection (decubitus ulcer, diabetic ulcer)
- Osteomyelitis

Noninfectious causes

- Postoperative
- Transfusion reaction
- Vascular (venous thromboembolism, thrombophlebitis, fat embolism)
- Central nervous system (subarachnoid hemorrhage, acute ischemic stroke, traumatic brain injury, central or hypothalamic fever)
- Abdominal (pancreatitis, acalculous cholecystitis)
- Endocrinologic (thyroid storm, pheochromocytoma, adrenal insufficiency)
- Malignancy (“B symptoms”)
- Autoimmune (vasculitis, polyarticular gout, adult-onset Still disease)
- Drug related (hypersensitivity reactions, chemotherapy, Jarisch-Herxheimer reaction, aspirin toxicity)
- Heat stroke (exertional and nonexertional)
- Others:
  - Transplant rejection
  - Acute respiratory distress syndrome
  - Alcohol intoxication/withdrawal
  - Rhabdomyolysis
  - Thrombotic thrombocytopenic purpura
- Hyperthermic syndromes:
  - Malignant hyperthermia (halothane, isoflurane, succinylcholine)
  - Serotonin syndrome (SSRIs, mixed reuptake inhibitors)
  - Neuroleptic malignant syndrome (antipsychotic phenothiazines: haloperidol, metoclopramide, and prochlorperazine)

- Anticholinergic toxicity (atropine, TCAs, antihistamines)
- Sympathomimetic poisoning (MAOIs, cocaine, amphetamines, methamphetamines)

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Damage to the hypothalamus from trauma, tumor, hemorrhage, or ischemia can raise the hypothalamic temperature set point, causing what is termed a *hypothalamic* or *central fever.* This is a true fever as opposed to a hyperthermic process. Clues to suggest a central fever include a plateau fever curve, poor response to antipyretics, lack of sweat, and suspected or confirmed hypothalamic injury. However, hypothalamic lesions are most commonly associated with hypothermia.

In contrast to fevers, hyperthermia refers to an increase in body temperature, despite normal thermoregulatory center (hypothalamic) activity, and can be due to increased heat production or decreased heat loss. Hyperthermia is not a normal physiologic response and, when left untreated, can result in serious morbidity and mortality. Common causes of hyperthermia include heat stroke (Table 34.2), endocrinologic etiologies (adrenal crisis, thyrotoxicosis, and pheochromocytoma), and medications, including certain illicit substances. Diagnosis of drug-induced hyperthermic syndromes can be made based on medication history and clinical signs (Table 34.3). See Chapter 36, Toxicology, for more information regarding these toxidromes.

TABLE 34.2 Features of Exertional and Nonexertional Heat Stroke

	Exertional	Nonexertional
Population	Young, typically healthy	Older age, prepubertal
	Strenuous activity	Sedentary behaviors
Time frame	Sporadic	Common in heat waves
Mechanism	Excessive heat production (gain)	Poor heat dissipation (loss)
Sweating	Typically profuse	Often absent
Clinical features	Temperature elevation >40.5 °C CNS effects: confusion, dizziness, lethargy, coma, seizures Cardiac, renal, and hepatic dysfunction Disseminated intravascular coagulation Acute respiratory distress syndrome Rhabdomyolysis	

CNS, central nervous system.

TABLE 34.3 Selected Drug-Induced Hyperthermic Syndromes

Clinical Syndrome	Associated Precipitants	Time Course	Signs/Symptoms	Complications	Notes

Clinical Syndrome	Associated Precipitants	Time Course	Signs/Symptoms	Complications	Notes
Malignant hyperthermia	Volatile anesthetic gases and depolarizing paralytics (halothane, isoflurane, succinylcholine)	Minutes to hours after exposure	Dramatically high fever, muscle rigidity, tachycardia, hypercarbia	Rhabdomyolysis, hemodynamic collapse, and death	Inherited defect in skeletal muscle calcium metabolism
Serotonin syndrome	Serotonergic pathway medications (SSRIs, MAOIs, SNRIs, TCAs), linezolid, fentanyl, meperidine, dextromethorphan	Hours after exposure	Triad: 1. Cognitive problems (confusion, agitation) 2. Autonomic instability 3. Neuromuscular abnormalities (clonus, hyperreflexia, and tremor)	Rhabdomyolysis, renal failure	Hyperthermia is present in ~50% and is due to increased muscle activity (agitation and tremor)
Neuroleptic malignant syndrome (NMS)	Neuroleptic medications (phenothiazines, haloperidol, metoclopramide, and prochlorperazine), or acute withdrawal of dopamine agonists (L-dopa)	Several hours to days after exposure	Hyperthermia, "lead-pipe" muscle rigidity, autonomic instability, and altered mental status (stupor, depression)	*Neuro:* seizures *Cardiac:* cardiac arrhythmias including torsades de pointes, cardiac arrest, MI, cardiomyopathy *Pulm:* respiratory failure, aspiration pneumonia, pulmonary embolism *Renal:* dehydration, electrolyte imbalance, ARF due to rhabdomyolysis *Heme:* DVT and phlebitis, thrombocytopenia, DIC, sepsis	Hyperthermia results from muscle activity and central hypothalamic dysregulation
Anticholinergic toxicity	Central and peripheral muscarinic receptor blockers (antihistamines, atropine, and TCAs)	Hours after exposure	confusion, tremor, hallucinations, mydriasis, xerostomia, constipation, urinary retention, and coma	Similar to NMS	Hyperthermia results from decreased sweating.

Clinical Syndrome	Associated Precipitants	Time Course	Signs/Symptoms	Complications	Notes
Sympathomimetic toxicity poisoning	MAOI and drugs of abuse (cocaine, amphetamine, methamphetamine, and derivatives, ie, ecstasy)	Hours after exposure	Hyperthermia, diaphoresis, tachycardia, ataxia, insomnia, rhabdomyolysis, and seizures	Cerebral edema, seizures, cardiac arrest, ARF	Serotonergic and dopaminergic pathways involved. Central and peripheral dysregulation leads to hyperthermia.

ARF, acute renal failure; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

TREATMENT

The priority in treating a patient with fever is to treat the underlying cause. The decision to pharmacologically or physically lower the body temperature is based on the cause, clinical situation, and severity of temperature elevation. Treatment options are listed in Table 34.4. There is no clear benefit to treating low-grade fevers, and treatment can mask characteristic disease-specific fever patterns, like the tertian and quartan fevers of plasmodium infections or the Pel-Ebstein fevers of lymphoma. Lowering the body temperature is warranted in cases of high fevers associated with mental status changes, seizures, and in critically ill patients with severe underlying pulmonary or cardiovascular disease. Hyperthermic syndromes typically do not respond well to antipyretic therapy and require removal of the inciting agent and targeted pharmacologic therapy as outlined in Table 34.4. In addition, external (or noninvasive) cooling methods should be started immediately, and severe cases may require internal (invasive) cooling methods.

TABLE 34.4 Therapeutic Options for Fever and Hyperthermia

- Antipyretics
  - Acetaminophen (preferred if no contraindications)
  - Nonsteroidal anti-inflammatory drugs
- External cooling
  - Cooling blankets
  - Sponging
  - Fans
  - Ice baths
- Internal cooling
  - Gastric or peritoneal lavage
  - Intravenous fluid replacement
  - Hemodialysis
  - Endovascular cooling catheter
  - Sedation with paralysis if necessary
- Drug-induced hyperthermia
  - Remove inciting agent
- Pharmacologic therapies (and specific indications)[a]
  - Dantrolene (MH and NMS)
  - Bromocriptine (NMS)

Cyproheptadine (SS)
Physostigmine (AS)
Procainamide (VF prophylaxis in NMS)

AS, anticholinergic syndrome; MH, malignant hyperthermia; NMS, neuroleptic malignant syndrome; SS, serotonin syndrome; VF, ventricular fibrillation.

[a]See common drug dosages and side effects in Appendix.

Hypothermia

Hypothermia is defined as core body temperature less than 35 °C (<95 °F). Table 34.5 lists possible causes. Excessive cold exposure is the most common etiology in emergency department settings, but severe sepsis, intoxications, and endocrinopathies are frequent causes seen in the ICU. The majority of cases occur in patients with chronic underlying illness, older patients, and in debilitated, homeless, or intoxicated patients.

TABLE 34.5 Causes of Hypothermia

Cold exposure
Fulminant sepsis
Drugs (alcohol intoxication, sedatives, general anesthetics, antihypertensives)
Endocrinologic disorders (hypothyroidism/myxedema coma, adrenal insufficiency, hypopituitarism)
Diabetic ketoacidosis
Multisystem trauma
Prolonged cardiac arrest
Kidney failure
Liver failure
Aggressive intravenous fluid replacement
Continuous or intermittent hemodialysis
CNS disorders (ischemic stroke, subarachnoid hemorrhage, trauma, hypothalamic dysfunction, spinal cord injuries)
Burns

CNS, central nervous system as table footnote.

Hypothermia can be divided into three grades of severity when based on a reliable core body temperature measurement: mild (32-35 °C [90-95 °F]), moderate (28-32 °C [82-90 °F]), and severe (<28 °C [<82 °F]). The characteristics of patients with mild hypothermia are shivering, cool extremities, and pallor. Shivering decreases as hypothermia worsens, and moderate-to-severe hypothermia is characterized by depressed mental status, ataxia, cardiac arrhythmias (ie, bradycardia or supraventricular arrhythmias), hyporeflexia, hypoventilation, dilated pupils, and peripheral vasoconstriction, resulting in impalpable pulses. Severe cases can lead to coma, pulmonary edema, cardiac arrest, and death.

Laboratory studies may include renal failure, liver dysfunction, acidosis, and coagulopathy. Typically, electrolyte changes are unpredictable. End-organ dysfunction results from decreased cardiac output and diminished clearance of toxins and drugs. Electrocardiographic (EKG) abnormalities include J (aka Osborn) waves and prolonged PR, QRS, and QT intervals. J waves are positive deflections at the QRS-ST junction in the left ventricular leads, can be found in up to 80% of patients with hypothermia, and may be mistaken for a new right bundle branch block. Unlike other EKG changes in hypothermia (which resolve with rewarming), J waves can persist for 12 to 24 hours after euthermia is restored.

TREATMENT

Initial treatment follows the ABCs (airway, breathing, circulation) of advanced cardiac life support and begins with the removal of wet clothing, protection from heat loss, and avoidance of excessive movement to prevent cardiac dysrhythmias. Patients should be connected to a cardiac monitor to identify the cardiac rhythm, as hypothermia-induced bradycardia and peripheral vasoconstriction can make palpation of peripheral pulses difficult.

Passive rewarming is usually sufficient for mild hypothermia, but aggressive active external and internal rewarming is the mainstay of therapy for more severe cases, as outlined in Table 34.6. The goal temperature increase is 1 to 2 °C (2-4 °F) per hour and should be monitored with a continuous core body temperature probe. More rapid rewarming may be necessary for patients in the event of cardiac arrest associated with severe hypothermia.

TABLE 34.6 Therapies for Hypothermia and Expected Change in Core Body Temperature

Warming Method	Temperature (°C/h)
Passive external	0.5-4
Blankets Warmed ambient environment Humidified inspired air	
Active external	1-4
Blankets (prewarmed or heated with forced air or fluid) Warm water immersion Warm water packs	
Active internal	Variable
Warmed (42 °C) humidified air Warmed (42 °C) intravenous fluids Body cavity lavage with warm saline (GI, bladder, peritoneal, pleural)	
Extracorporeal	
Hemodialysis/hemofiltration	2-3
Continuous arteriovenous rewarming	3-4
Cardiopulmonary bypass	7-10

GI, gastrointestinal.
Modified from Aslam AF, Aslam AK, Vasavada BC, et al. Hypothermia: evaluation, electrocardiographic manifestations, and management. *Am J Med.* 2006;119(4):297-301, with permission.

Active external rewarming alone can cause temperature “afterdrop” as cold peripheral blood is circulated back to the core. This can be avoided by the concomitant use of internal rewarming. Hypotension may occur during rewarming due to reactive peripheral vasodilation. Patients should, therefore, be treated with warm intravenous fluids, and blood pressure should be monitored frequently. Continuous cardiac monitoring and frequent serum electrolyte tests with prompt correction can help with early detection of and minimize the risk for arrhythmias.

As hypothermia progresses, the risk of cardiac arrhythmias increases, and these arrhythmias may become refractory to cardioversion. In addition, cardiovascular drug efficacy

is reduced, and metabolism is decreased in patients with hypothermia. Advanced cardiac life support management should be modified in these circumstances. When the core temperature is less than 30 °C and ventricular tachycardia or fibrillation occurs, a single initial defibrillation attempt is appropriate, but further attempts should be withheld until the core temperature is increased to more than 30 °C. Similarly, cardioactive medications should be held until body temperatures rise above 30 °C, and when given, the frequency of drug administrations should be decreased to avoid toxic buildup.

The prognosis depends on cause, comorbidities, and complications. Mortality rates up to 100% are reported in the most severe cases, but death should not be proclaimed until the patient has been successfully rewarmed.

In patients affected by frostbite, affected body parts should be manipulated as little as possible. Affected areas should be thawed by warm water immersion, no warmer than 40 to 42 °C. Water above this temperature can cause additional damage. Blisters may form during the rewarming process. Clear blisters can be debrided to avoid continued tissue damage, but hemorrhagic blisters should be left intact to avoid infection. Thawed body parts should be kept on sterile sheets and evaluated by a surgeon to assess tissue viability. Urgent amputation is rarely indicated, but patients should be monitored frequently for the development of compartment syndrome.

Induced Hypothermia as Therapy

Iatrogenic hypothermia may help minimize the neurologic sequelae due to ischemia-reperfusion injury. Induced hypothermia, often to a temperature of 32 to 34 °C, following out-of-hospital cardiac arrest has been practiced in some centers since the early 2000s based on data from a few small trials. However, recent larger studies have failed to demonstrate a benefit. Contemporary guidelines recommend the active maintenance of normothermia, including active cooling if needed to maintain a temperature of less than 37.5 °C in these cases. Additional details regarding targeted temperature management in post–cardiac arrest care can be found in Chapter 25, Post—Cardiac Arrest Management. Similarly, the benefit of induced hypothermia in adults with acute ischemic stroke and traumatic cerebral edema is unclear, but some centers may use induced hypothermia for patients with increased intracranial pressures refractory to first-line therapies.

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35 High-Altitude Illness

Nguyet Nguyen

Travel or rapid ascent to new high elevations without adequate time for the body to acclimate may lead to the development of high-altitude illness (HAI). HAI includes acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). HAI results from hypoxic stress at high altitudes, with the main characteristic being extravascular fluid accumulation in the brain (AMS/HACE) and lungs (HAPE). The threshold altitude for HAI is commonly 2,500 m, but some may experience HAI at lower altitudes, ranging from 1,500 to 2,100 m. HAI affects individuals of all ages and genders, regardless of fitness. Susceptibility to HAI cannot be determined before exposure to high altitude, but risk factors include a past history of HAI, rapid ascent (<24 hours) from low altitude to a sleeping altitude greater than 2,750 m, rapid ascent of more than 500 to 1,000 m/d from altitudes above 2,750 m, substances that interfere with acclimatization (alcohol or sedatives), comorbidities that interfere with respiration (neuromuscular disease, severe obstructive sleep apnea (OSA), moderate-to-severe chronic obstructive pulmonary disease [COPD], cystic fibrosis [CF]) or circulation (angina, congestive heart failure [CHF], sickle cell, or pulmonary hypertension), and overexertion prior to acclimatization. The onset of HAI can occur anywhere from 6 to 12 hours to 5 days after arrival at high altitude, with symptoms ranging from mild to life threatening.

Acute Mountain Sickness/High-Altitude Cerebral Edema

AMS is the most common HAI, with prevalence and severity increasing with altitude. In unacclimatized persons, AMS occurs in 10% to 25% of those ascending to 2,500 m and 50% to 85% of those ascending to 4,500 to 5,500 m. Headache is the cardinal symptom and can be accompanied by any combination of the following: fatigue, dizziness, malaise, nausea, anorexia, and sleep disturbances. Symptoms usually resolve after 1 to 2 days if there is no further ascent. While symptoms do not recur at the same altitude, they can reappear with ascent to higher altitudes. AMS treatment depends on severity: mild illness responds to symptomatic treatment with analgesics and antiemetics, avoiding further ascent, and limiting exercise; moderate-to-severe symptoms may require dexamethasone (4 mg by mouth [PO] or intramuscular [IM] every 6 hours for 1-2 days), supplemental oxygen, or descent. If AMS symptoms do not respond to treatment or worsen, HACE should be suspected, and descent is indicated. Experts consider AMS and HACE to represent a spectrum of illness with common pathophysiology. AMS often precedes HACE but is not required for HACE. The hallmark symptoms of HACE are encephalopathy, truncal ataxia, and usually a mild fever. Other symptoms include those seen with AMS, lassitude, irritability, and a progressive decline of mental function and consciousness. HACE is unpredictable and can develop in 12 hours to 3 days, with a tendency to develop faster in those with concurrent HAPE. HACE requires immediate intervention with descent as the definitive treatment; a descent of 1,000 m is usually lifesaving. Dexamethasone (8-10 mg PO/intravenous [IV]/IM followed by 4 mg every 6 hours) is used as a rescue medication until descent can be achieved but is not a substitute for descent. Oxygen (2-4 L) should be administered to maintain SpO_2 greater than 90%. Hyperbaric therapy in a portable, manually inflated chamber is lifesaving if a patient with HACE is unable to be immediately transported to lower elevations. If HACE is untreated or advanced to an irreversible stage prior to descent, HACE is fatal.

High-Altitude Pulmonary Edema

HAPE is a form of noncardiogenic pulmonary edema that develops 2 to 4 days after rapid ascent above 2,500 m and rarely occurs after 1 week at the same altitude. Like HACE, HAPE is often preceded by AMS, can occur alone or with AMS/HACE, can recur with repeat ascent to the same elevation, and is the most common cause of death among HAIs. At high altitudes, hypobaric hypoxia leads to increased sympathetic tone, inadequate production of endothelial nitric oxide, overproduction of endothelin, uneven pulmonary vasoconstriction, and pulmonary hypertension. Elevated pulmonary artery pressure is essential for the development of HAPE, with mean pulmonary artery pressures usually higher than 35 to 40 mm Hg. Uneven pulmonary vasoconstriction and regional overperfusion from pulmonary hypertension result in leakiness of the alveolar-capillary barrier, leading to patchy pulmonary edema. Initial symptoms include a nonproductive cough and shortness of breath with exertion. Early progression from dyspnea with exertion to dyspnea at rest is a cardinal feature of HAPE. Cough and dyspnea worsen, followed by orthopnea and the production of pink, frothy sputum. Clinical examination will show cyanosis, tachypnea, tachycardia, and low-grade fever, with crackles first heard in the right middle lobe. Chest imaging will show patchy alveolar infiltrates predominantly in the right central hemithorax that become bilateral and confluent with time. A distinct finding in HAPE is that the patient does not appear as ill as the radiograph would suggest, and there is a steady improvement with oxygen therapy. If a chest radiograph is not possible, ultrasound of lungs will show B-lines consistent with pulmonary edema. Patients with HAPE have severe hypoxemia with Spo_2 ranging from 50% to 75% and Po_2 from 25 to 40. Despite these low numbers, the patient will not appear as clinically ill as the numbers would suggest, and they improve rapidly with supplemental oxygen. A history of a recent increase in altitude, together with extreme hypoxia, and rapid improvement after 1 to 2 hours of oxygen will help make the diagnosis of HAPE more likely. Treatment

of HAPE depends on the severity of illness and the availability of resources, and oxygen, if available, is the first-line therapy. Rest and warmth should also be provided as these measures decrease pulmonary artery pressure. If oxygen is not available, then descent should begin as soon as HAPE is suspected. Hyperbaric therapy can also be used if oxygen is not available. Nifedipine (30 mg slow release every 12 hours) can be used if oxygen is not available and conditions do not allow for a safe descent. Descent is mandatory at elevations above 4,000 m. Oxygen and descent (or hyperbaric chamber) are superior to pharmacologic treatment.

Prevention

Prevention of AMS, HACE, and HAPE can be achieved with gradual or staged ascent. Pharmacologic prevention should be reserved for individuals at high or moderate risk with a history of AMS/HACE when rapid ascent cannot be avoided. Acetazolamide, at a dose of 125 mg every 12 hours, can reduce symptoms by 75%. The drug should be started the day before ascent and continued for 48 hours. It can also be taken to speed acclimatization at any altitude. For those allergic to acetazolamide, dexamethasone at a dose of 2 mg every 6 hours or 4 mg every 12 hours is sufficient. Nifedipine (30 mg every 12 hours) is the drug of choice for prophylaxis against HAPE in high-risk individuals when rapid ascent cannot be avoided. Dosing should start 24 hours prior to ascent and continued for 5 days at the destination altitude. In small studies, dexamethasone, tadalafil, and sildenafil have all been used as prophylaxis with good result, but more studies need to be conducted for dexamethasone, and optimal doses have not been established for tadalafil and sildenafil.

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SECTION IX TOXICOLOGY

36 Toxicology

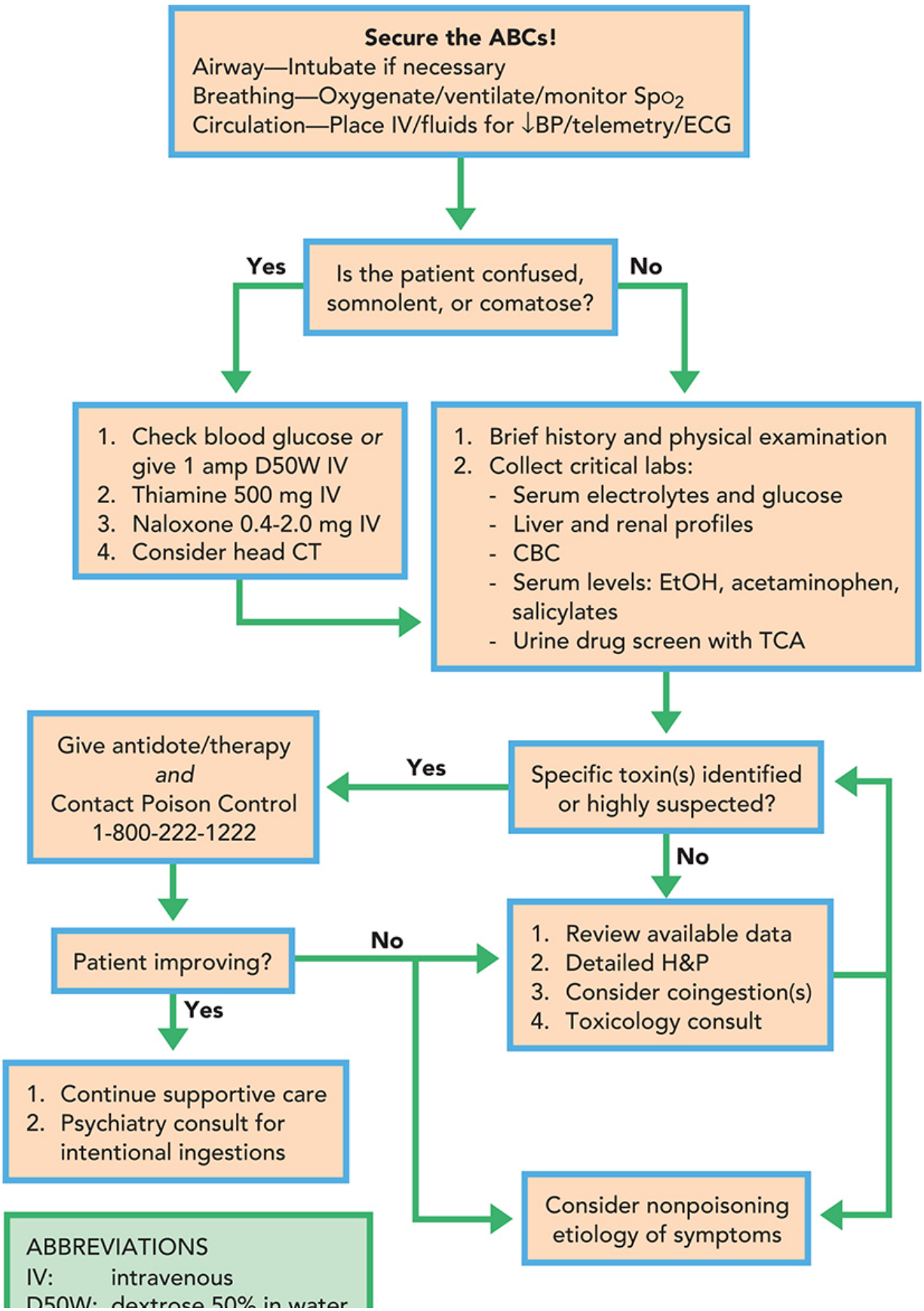
Brian P. Frodey and Steven L. Brody

More than 2 million cases of accidental or intentional poisoning were recorded by the U.S. poison control centers in 2021. Among fatalities, 92% were 20 years of age or older. The most commonly reported fatal drug poisonings were acetaminophen alone or in combination, calcium channel blockers or beta-blockers, opioids, alcohols, sedatives/hypnotics/antipsychotics, antidepressants, and stimulants. Intensive care unit (ICU) admissions for management of severe antidepressant and opioid intoxications are common. Although much of the initial management is provided in the emergency department (ED), critical care physicians often subsequently manage the poisoned patient. In addition, the intensivist may encounter iatrogenic intoxications due to drugs used in the hospital and ICU.

Key Steps in the Management of the Poisoned Patient

Algorithm 36.1 presents an outline for managing the poisoned patient.

ALGORITHM 36.1 **Key Steps in the Initial Management of the Poisoned Patient**


Secure the ABCs!
Airway—Intubate if necessary
Breathing—Oxygenate/ventilate/monitor Spo_2
Circulation—Place IV/fluids for ↓BP/telemetry/ECG
Is the patient confused, somnolent, or comatose?
Yes
No
1. Check blood glucose *or* give 1 amp D50W IV
2. Thiamine 500 mg IV
3. Naloxone 0.4-2.0 mg IV
4. Consider head CT
1. Brief history and physical examination
2. Collect critical labs:
- Serum electrolytes and glucose
- Liver and renal profiles
- CBC
- Serum levels: EtOH, acetaminophen, salicylates
- Urine drug screen with TCA
Specific toxin(s) identified or highly suspected?
Yes
No
Give antidote/therapy *and* Contact Poison Control 1-800-222-1222
Patient improving?
No
Yes
1. Review available data
2. Detailed H&P
3. Consider coingestion(s)
4. Toxicology consult
1. Continue supportive care
2. Psychiatry consult for intentional ingestions
Consider nonpoisoning etiology of symptoms
ABBREVIATIONS
IV: intravenous
D50W: dextrose 50% in water

D50W:	dextrose 50% in water
CT:	computed tomography
CBC:	complete blood count
EtOH:	ethanol
TCA:	tricyclic antidepressant
H&P:	history and physical examination
ABC:	airway, breathing, and circulation
Spo_2:	peripheral capillary oxygen saturation
BP:	blood pressure

1. Before all else, address the “ABCDEs” (airway, breathing, circulation, disability, and exposure/examination).
   - Provide oxygen, intubate, and mechanically ventilate for airway protection or respiratory failure.
   - Obtain intravenous (IV) access and initially give crystalloid for hypotension. Obtain electrocardiogram (ECG) and routine labs. Obtain extra tubes of blood for serum drug and toxin levels.
   - Expose patient and perform a secondary trauma survey.
2. Treat potentially reversible causes of altered mental status or coma with:
   - rapid glucose assessment and treatment, if indicated.
   - thiamine 500 mg IV, if suspected Wernicke encephalopathy.
   - Naloxone 0.4 to 2.0 mg IV/IM (intramuscular) or 2.0 to 4.0 mg intranasal, if possible opioid toxicity.
3. Assess for and treat toxidrome (Table 36.1). Give specific antidotes or therapy when indicated (Table 36.2). Call the regional Poison Control Center at 1-800-222-1222 for management advice.
4. Block absorption of toxins when appropriate (see “Gastric Decontamination” section).
5. Enhance elimination of toxins when appropriate (see “Enhancing Drug Elimination” section).

TABLE 36.1 Clinical Toxidromes

Toxidrome	Features	Offending Agents
Sympathomimetic	Hypertension, tachycardia, tachypnea, hyperthermia, mydriasis, agitation, hallucinations, diaphoresis	Cocaine Amphetamines 3,4-Methylenedioxymethamphetamine (MDMA) Synthetic cathinones “Bath salts” Cannabinoids Theophylline Caffeine Ephedrine Pseudoephedrine Caffeine-containing “energy drinks”
Anticholinergic “hot as a hare, dry as a bone, red as a beet, mad as a hatter”	Hypertension, tachycardia, tachypnea, hyperthermia, mydriasis, agitation, delirium, hallucinations, dry skin, dry mouth, ileus, urinary retention	Tricyclic antidepressants Antihistamines Atropine Phenothiazines Scopolamine Belladonna alkaloids
Cholinergic “SLUDGE”	Salivation, lacrimation, urination, diarrhea, gastrointestinal distress, emesis; also bronchorrhea, bronchoconstriction, bradycardia, miosis, confusion, coma	Organophosphates Physostigmine Pyridostigmine Edrophonium

Toxidrome	Features	Offending Agents
Opioid	Hypotension, bradycardia, hypopnea, bradypnea, hypothermia, miosis, CNS depression/coma, decreased bowel sounds, pulmonary edema	Heroin Oxycodone Morphine Meperidine Fentanyl Codeine Methadone Loperamide
Sedative-hypnotic	Hypotension, bradycardia, hypopnea, bradypnea, CNS depression, coma	Benzodiazepines Barbiturates Alcohols
Extrapyramidal	Rigidity, torticollis, opisthotonos, trismus, oculogyric crisis, dysphoria	Prochlorperazine Haloperidol Chlorpromazine Other antipsychotics
Serotonin syndrome	Triad of cognitive (agitation, confusion), autonomic (hyperthermia, diarrhea, nausea, mydriasis), and somatic (myoclonus, hyperreflexia) symptoms	Monoamine oxidase inhibitors Selective serotonin reuptake inhibitors (SSRIs) Serotonin-norepinephrine reuptake inhibitors (SNRIs) Atypical antidepressants Tricyclic antidepressants Opioids (Fentanyl) Amphetamines Cocaine Linezolid

CNS, central nervous system.

TABLE 36.2 Specific Antidotes for Selected Toxins

Toxin	Antidotes

Toxin	Antidotes
Acetaminophen	*N*-Acetylcysteine (see Table 36.11)
Beta-blocker/calcium channel blockers	Atropine 0.5 mg q3-5min, max 3 mg Calcium chloride 1 g IV (calcium gluconate 3 g IV), q10-20min, max 3 g calcium chloride (9 g calcium gluconate) Glucagon 5-10 mg IV bolus followed by 1-10 mg/h infusion Regular insulin 1 unit/kg IV bolus followed by 0.5-10 units/kg/h IV infusion (with dextrose) Vasopressors Intralipid 20% 1.5 mL/kg bolus followed by 0.25-0.5 mL/kg/min until recovery of vital signs Consider cardiac pacing, extracorporeal life support.
Carbon monoxide	100% O_2, hyperbaric O_2 in some cases
Cholinesterase inhibitors (eg, organophosphates)	Atropine 1-3 mg IV, double dose q5min until resolution of wheezing and bronchorrhea, followed by infusion (10%-20% of loading dose/h, typical max 2 mg/h) Pralidoxime 30 mg/kg (max 2 g) over 30 min, followed by 8-10 mg/kg/h IV infusion (max 650 mg/h)
Cyanide	Hydroxocobalamin 5 g IV over 15 min, may repeat Sodium nitrite 300 mg IV over 2-5 min Sodium thiosulfate 12.5 g in 50 mL vial IV over 10 min (caution hypotension, methemoglobinemia, hypersensitivity reaction)
Digoxin	Digoxin-specific antibody fragments (Fab) Acute: 10-20 vials; chronic: 3-6 vials
Ethylene glycol Methanol	Fomepizole 15 mg/kg IV over 30 min (first dose), then 10 mg/kg q12h × 4 doses, then 15 mg/kg q12h as needed
Iron	Deferoxamine start at 5 mg/kg/h, titrate as tolerated to 15 mg/kg/h, max daily dose 6-8 g/24 h

Toxin	Antidotes
Methemoglobinemia (several drugs)	Methylene blue 1-2 mg/kg IV over 5 min followed by 30 mL saline flush
Opioids	Naloxone 0.04-2 mg IV (IM, SC, intranasal, or endotracheally)
Sulfonylureas	Octreotide 50 mcg SC q6h, dextrose 10% IV
Snake bite	CroFab 4-6 vials in 250 mL normal saline, infused over 1 h. Double the dose if shock or serious active bleeding. Reevaluate every 15 min for progression of symptoms and repeat dosing until symptoms are reversed. Call physician expert.
Tricyclic antidepressants	Sodium bicarbonate 1-2 mEq/kg bolus, q3-5min, until resolution of ECG changes or hypotension, target pH # 7.55, followed by 150 mEq in 1 L of D5W at twice maintenance fluid rate up to target pH # 7.55 Intralipid 20% 1.5 mL/kg bolus followed by 0.25-0.5 mL/kg/min until recovery of vital signs

D5W, dextrose 5% in water; ECG, electrocardiogram; IM, intramuscularly; IV, intravenously; SC, subcutaneously.

Initial Evaluation

The initial assessment of the poisoned patient should begin with the ABCDEs: airway, breathing, circulation, disability, and exposure/examination. Respiratory depression, loss of airway protective reflexes, and aspiration are common consequences of ingestion. Awake patients may need close monitoring for delayed drug effects. Lethargic patients or those with recurrent seizures may require endotracheal intubation. When in doubt, the airway should be secured by intubation.

Ventilatory failure in the poisoned patient may be a consequence of aspiration, respiratory depression (eg, from sedatives), muscle

paralysis/weakness (eg, from botulism), or pulmonary edema. Arterial blood gas (ABG) measurement may reveal an elevated $Paco_2$ as a marker of early respiratory failure. Somnolence in the setting of a rising $Paco_2$ is an indication for intubation.

Hypotension, arrhythmias, and circulatory failure/shock can occur with poisonings. Venous access should be obtained and IV fluids given for hypotension. Continuous ECG monitoring should be initiated and an ECG obtained. Some common therapies for arrhythmias should be avoided with certain intoxications (eg, beta-blockers in cocaine intoxication). Patients who are pulseless or hemodynamically unstable should initially receive standard advanced cardiac life support therapies. However, toxin-induced cardiac arrest may require specific therapies. For example, suspected calcium channel blockers should be preferentially treated with adrenergic agonists, IV calcium, and high-dose insulin. Extracorporeal life support for refractory hypotension or cardiac arrest may be considered in certain cases.

Patients should then be exposed and examined for signs of a specific toxidrome (Table 36.1). Key examination components include assessment of pupils, reflexes, muscular tone, perspiration, and skin changes. A head computed tomography (CT) scan should be considered for those with altered mental status.

Diagnostic Strategies

IMPORTANT PRINCIPLES

- All overdoses are considered polysubstance overdoses until proven otherwise. Ethanol and opiates are common components of polysubstance overdose.
- The following lethal ingestions with specific therapies should always be ruled out:
  - Acetaminophen (serum level)
  - Tricyclic antidepressants (TCAs) and antipsychotics (ECG)

    - Salicylates (serum level)
- Preexisting illnesses and coingestions can confound a “classic” poisoning presentation.
- Toxins screened on “drug screens” vary among institutions and are often insensitive and nonspecific. Avoid reliance on drug screens in the face of a clinical toxidrome.

TOXIDROMES

A *toxidrome* is a constellation of signs and symptoms that may be seen after exposure to a specific class of intoxicant (Table 36.1). The physical examination should be performed with attention to vital signs, mental status, pupillary size, and psychomotor state that suggest a specific toxidrome.

INGESTION HISTORY

An accurate accounting of the ingestion should be obtained. Details including drug name, formulation (eg, sustained release, dosage form), time of ingestion (acute or chronic), and quantity of ingestion should be sought. Inquire as to possible over-the-counter medications, herbal treatments, or drugs prescribed for others that may be accessible to the patient. An outpatient medication record should be established. Relevant details may come from first responders (eg, emergency medical services) or patient contacts. Be aware that the history obtained may be unreliable or incomplete.

OPTIMAL USE OF LABORATORY TESTS

Basic tests should include a comprehensive metabolic panel, complete blood cell count, coagulation studies, serum osmolality, ethanol, acetaminophen, and salicylate levels. Arterial blood should be analyzed by co-oximetry in the presence of respiratory distress, altered mental status, somnolence, coma, or cyanosis. Serum levels of digoxin, lithium, theophylline, phenytoin, and iron should be obtained if the patient is known to take or have immediate access to

these medicines. Do not delay treatment awaiting test results if a toxic ingestion is suspected.

Be cautious with the use and interpretation of urine toxicology screening tests. Many substances are not included on screens for drugs of abuse, and other substances may be present but not causative of the patient's signs or symptoms. Further, depending on the timing of the ingestion, coingestions, and the test used, results may be falsely negative or falsely positive. Some tests evaluate for metabolites of a drug and others test for only some drugs in a particular drug class (eg, some opiate screens are negative in the presence of methadone or fentanyl). Thus, toxicology screening tests may support clinical suspicion, but management and therapy should be guided by a careful history, examination, identification of a toxidrome, and clinical findings.

EVALUATION OF LABORATORY ABNORMALITIES

Clues to specific poisonings may be found by attention to the "three gaps":

Anion gap elevations may indicate the ingestion of toxins such as ethylene glycol, methanol, or salicylates. The formula for calculating the serum anion gap is as follows and causes of an elevated or low anion gap are included in Table 36.3.

$$\text{Anion gap} = [Na^+] - [Cl^-] + [HCO_3^-]$$

TABLE 36.3 Selected Causes of an Elevated Anion Gap

Toxic Ingestions	Other Causes

Toxic Ingestions	Other Causes
Ethylene glycol Iron Isoniazid Methanol Oxoproline (acetaminophen use) Paraldehyde Salicylate	Alcoholic ketoacidosis Diabetic ketoacidosis Starvation ketosis D-Lactate Lactic acidosis Oxoproline (starvation) Uremic acidosis
Selected causes of a low anion gap	
Elevated immunoglobulin G (IgG, eg, multiple myeloma) Hypoalbuminemia	Hypercalcemia Hypermagnesemia Lithium

The normal range is 8 to 13 mEq/L and varies with albumin level.

Osmolal gap elevations may be present following toxic ingestions of alcohol. The serum osmolal gap is the difference between the measured and calculated serum osmolality. An elevated osmolal gap reflects the presence of an osmotically active substance in the blood that is not accounted for by routine calculation of osmolality. Formulas necessary for calculating the osmolal gap are as follows, and a list of causes of an elevated osmolal gap is included in Table 36.4.

$$Osm_{calculated} = 2[Na^+] + [urea]/2.8 + [glucose]/18 + [ethanol]/4.6$$

where $[Na^+]$ is in mmol/L and [urea], [glucose], and [ethanol] are in mg/dL.

$$\text{Osmolal gap} = Osm_{measured} - Osm_{calculated} \text{ (normal <10)}$$

TABLE 36.4 Selected Causes of an Elevated Osmolal Gap

With Normal Anion Gap	With Elevated Anion Gap

With Normal Anion Gap	With Elevated Anion Gap
Isopropanol	Methanol
Acetone	Ethylene glycol
Mannitol	Formaldehyde
Ethanol	Propylene glycol

Oxygen saturation gap describes differences between oxyhemoglobin percentages as measured by pulse oximetry (Spo_2) or as estimated from arterial oxygen tension (Pao_2) when compared with the oxyhemoglobin percentage (Sao_2) as measured by co-oximetry. An oxygen saturation gap may indicate poisoning from carbon monoxide (CO), cyanide, hydrogen sulfide, or the presence of methemoglobinemia. If these toxins are suspected, arterial blood must be analyzed by a co-oximeter, which is capable of measuring the concentrations of oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin (COHb) in the specimen.

Treatment Strategies

ANTIDOTES

Specific antidotes are available for relatively few toxins. Although potentially lifesaving, many of these antidotes have adverse effects and can be harmful if used inappropriately. Consultation with a poison control center or a medical toxicologist is advised when prescribing an antidote with which one is unfamiliar. A select list of antidotes is included in Table 36.2.

GASTRIC DECONTAMINATION

Activated charcoal and whole-bowel irrigation (WBI) are methods for limiting the absorption of drugs in the gastrointestinal (GI) tract, when

used in the appropriate circumstances. Induced emesis and cathartics are not recommended because of the lack of proven efficacy and interference with enterally administered antidotes. Gastric lavage is rarely indicated but can be considered in large ingestions of a highly toxic and sustained-release medication.

Activated charcoal adsorbs many toxins to prevent systemic toxicity. Its efficacy is greatest in the first hour postingestion and is generally ineffective after 4 hours postingestion. Alcohols, metals (eg, iron), corrosives (acids and alkalis), and inorganic ions (eg lithium) are not well adsorbed by activated charcoal. The recommended single dose of activated charcoal is 1 g/kg premixed with sorbitol, PO/PT. Some toxins may benefit from repeated doses of activated charcoal. Potential indications and dosing for multiple-dose activated charcoal (MDAC) are provided in Table 36.5. Clinical outcome data surrounding the use of MDAC are limited. Contraindications to the administration of single-dose activated charcoal or MDAC are included in Table 36.5.

TABLE 36.5 Potential Indications for Multiple-Dose Activated Charcoal (Severe Poisoning) and Dosing

Indications
Massive pill overdoses of sustained release and/or highly toxic substances
Carbamazepine
Phenobarbital
Dapsone
Quinine
Theophylline

Indications
Limited evidence for use in overdoses of amiodarone, amitriptyline, colchicine, digoxin, disopyramide, duloxetine, lamotrigine, nadolol, phenytoin, quetiapine, quinine, sotalol, valproic acid, and verapamil. Consultation with expert in these cases is recommended.
Contraindications
Aspiration risk with unprotected airway
Hydrocarbon ingestion
Bowel obstruction or perforation
Need for endoscopy
Coadministration of cathartic with activated charcoal
Dosing
Dosing regimens vary. A typical regimen is 1 g/kg loading dose, followed by 0.5 g/kg every 4-6 h, for 12-24 h (ideally by nasogastric tube).

WBI is the enteral administration of large volumes of an osmotically balanced polyethylene glycol electrolyte solution to induce rapid expulsion of unabsorbed toxins from the GI tract. No controlled studies have been published, but WBI may be considered in the management of certain ingestions (Table 36.6).

TABLE 36.6 Potential Indications for Whole-Bowel Irrigation and Dosing

Indications
Iron poisoning
Lithium poisoning

Indications
Sustained-release or enteric-coated medication toxicity
Retained illicit drug packets (ie, from “body packing”)
Contraindications
Unprotected airway
Bowel obstruction or perforation
Ileus
Uncontrolled vomiting
GI hemorrhage
Hemodynamic instability
Toxic colitis
Dosing
1,500-2,000 mL/h of polyethylene glycol electrolyte solution (PEG-ES) (ideally using nasogastric tube), continued until the rectal effluent is clear.

GI, gastrointestinal.

ENHANCING DRUG ELIMINATION

Urine alkalinization is a method of enhancing the renal elimination of certain poisons by increasing urine pH to levels greater than 7.5 through the administration of IV sodium bicarbonate. The strongest indication is moderately severe salicylate toxicity not meeting the criteria for hemodialysis. Other possible indications, contraindications, and dosing are included in Table 36.7.

TABLE 36.7 Potential Indications for Urine Alkalinization and Dosing

Indications
Salicylates: Severe cases not meeting criteria for hemodialysis
Methotrexate: Leucovorin, glucarpidase, and extracorporeal removal should be considered.
Phenoxy herbicides: Symptomatic poisonings, acidosis, hyperthermia
Chlorpropamide: Octreotide and dextrose infusion alone usually adequate
Phenobarbital: Multiple-dose activated charcoal may be more effective.
Fluoride: Hemodialysis should be considered in severe cases or with AKI.
Contraindications
Renal failure
Dosing
1-2 mEq/kg IV sodium bicarbonate bolus, followed by 150 mEq sodium bicarbonate (8.4%) in 1 L D5W infusion at 1.5-2 times maintenance fluid rate
Monitor
Urine pH (q1h initially) for goal 7.5-8.0
Serum pH (q2-4h) goal of 7.45-7.55
Serum electrolytes (q2-4h) with correction of any hypokalemia to achieve adequate alkalinization
Evaluate for complications of therapy including alkalemia, hypernatremia, volume overload, hypocalcemia, and hypokalemia

AKI, acute kidney failure.

Hemodialysis and hemoperfusion are extracorporeal methods of toxin removal that may be required to treat life-threatening toxicity (Table 36.8). General indications for use include clinical deterioration despite intensive alternative therapy, impairment of normal toxin elimination capacity (eg, liver or renal failure), and severe toxicity from drugs that can be removed faster by extracorporeal methods than by other means. Prompt nephrology and medical toxicology consultation should be obtained when hemodialysis or hemoperfusion is being considered.

TABLE 36.8 Selected Toxins Removable by Hemodialysis or Hemoperfusion

Drug	Indications
Acetaminophen	Serum acetaminophen level >900 mg/L with altered mental status, acidosis, and elevated lactate
Barbiturates[a]	Prolonged coma, refractory shock, mechanical ventilation, persistent toxicity, or rising levels despite MDAC
Beta-blockers	Limited to atenolol and sotalol poisoning with impaired renal function and refractory hypotension, bradycardia, or arrhythmias. Insufficient data for efficacy for removal of other beta-blockers
Carbamazepine[a]	Refractory seizures, life-threatening arrhythmias, prolonged coma, mechanical ventilation
Ethylene glycol	Serum anion gap >23 mmol/L, impaired renal function, level >50 mmol/L, osmolal gap >50, coma, seizures, or worsening clinical status
Isopropanol	Hypotension, clinical worsening, level >400 mg/d
Lithium	Serum Li >5.0 mEq/L or Li >4.0 mEq/L with impaired renal function, renal failure, coma, seizures, cardiovascular instability, confusion
Methanol	Coma, seizures, new visual deficit, pH #7.15, serum anion gap >24 mmol/L, impaired renal function, level >70 mg/dL, persistent acidosis despite standard therapy

Drug	Indications
Salicylates	Serum salicylate level >90 mg/dL, altered mental status, impaired renal function, new hypoxemia, clinical deterioration, severe acidemia (pH #7.20), or electrolyte disturbances despite standard therapy
Theophylline	Seizures, arrhythmias, persistent hypotension, clinical deterioration, level >100 mg/L in acute exposures, level >60 mg/L in chronic exposure, or rising levels despite optimal treatment
Valproic acid[a]	Shock, cerebral edema, mechanical ventilation, acute hyperammonemia, pH <7.10, level >900 mg/L

[a]Hemoperfusion is an acceptable alternative to hemodialysis.
MDAC, multiple-dose activated charcoal.

IV lipid emulsion (eg, lipid parenteral nutrition, 20% lipid) is the first-line treatment in local anesthetic toxicity. The American Society of Anesthesiology currently recommends 1.5 mL/kg bolus of 20% lipid followed by a 0.25 mL/kg/min infusion until hemodynamic stability is achieved. Emerging evidence suggests a possible role for IV lipid emulsion in overdoses with lipophilic drugs (eg, amitriptyline, bupropion) not responsive to standard therapies. It is theorized that the IV lipid sequesters toxins from physiologic binding sites.

APPROACH TO POISONING ASSOCIATED ORGAN FAILURE IN THE INTENSIVE CARE UNIT

Patients who are unstable and critically ill may be managed in the ICU for acute organ failure as a result of poisoning or intoxication (Table 36.9). Patients may rapidly develop shock, respiratory failure, coma, seizures, or hepatic failure demands specific intervention owing to a known toxin or will require a broad approach in the case of an unknown poison or exacerbation of an underlying chronic disease. The approach should initially be to review the “Key Steps in the Management of the Poisoned Patient” described at the top of the

chapter. Likewise, a review of “Diagnostic Strategies” may focus the acute treatment. General treatments are described in Table 36.9.

TABLE 36.9 Management of Common Toxin-Induced Acute Organ Failure in the Intensive Care Unit

Organ Failure	Potential Toxins	General Management
Bradycardia and shock	Beta-blockers and calcium channel blockers Digoxin	Atropine, IV calcium, high-dose insulin euglycemic therapy, glucagon, vasopressors Digoxin-specific antibody (Fab) fragments
Acute respiratory failure	Hypoventilation (opiates, sedative-hypnotics) Aspiration pneumonitis Acidosis (salicylates, ethylene glycol, methanol, etc) Tissue hypoxia (carbon monoxide, cyanide, methemoglobinemia) Pulmonary edema (opiates, naloxone, calcium channel blockers)	Naloxone and airway management Empiric antibiotics Targeted therapeutics (eg, fomepizole), sodium bicarbonate, hemodialysis 100% FIO_2, targeted therapeutics (hydroxocobalamin, methylene blue) Positive pressure (noninvasive or invasive) with treatment of underlying cause
Wide complex tachycardia	Sodium channel blockade (tricyclic antidepressants, cocaine, diphenhydramine, etc)	IV sodium bicarbonate
Coma	Sedative-hypnotics (ethanol, benzodiazepines, barbiturates)	Airway protection

Organ Failure	Potential Toxins	General Management
Seizures and status epilepticus	Withdrawal (benzodiazepines, ethanol) or excitatory (serotonin syndrome, sympathomimetics)	Glucose check/administration, benzodiazepines, propofol
Acute hepatic failure	Acetaminophen	*N*-Acetylcysteine

F_{IO_2}, fraction of inspired oxygen; IV, intravenous.

In addition to the patient admitted from the community with poisoning, drugs frequently used in the ICU may result in toxicity from drug combinations (eg, linezolid contributing to serotonin syndrome), sedatives (eg, opiates, gabapentin), propofol infusion syndrome, and others (Table 36.10). The toxins described later are selected as those commonly managed in the ICU including common medications, drugs of abuse, and environmental exposures.

TABLE 36.10 Hospital-Acquired Intoxications

Drug	Clinical Setting and Symptoms	Management
Propofol infusion syndrome	History of propofol infusion with hypertriglyceridemia, lactic acidosis, hyperkalemia, renal failure, rhabdomyolysis, cardiac arrhythmias, and progressive cardiovascular collapse. Associated with high mortality (30%-50%)	Discontinue propofol Supportive care that may include renal replacement therapy and extracorporeal life support.
Gabapentin	Confusion or lethargy, recent change in renal function	Discontinuation of medication Hemodialysis

Drug	Clinical Setting and Symptoms	Management
Propylene glycol intoxication	Prolonged infusion with medication containing propylene glycol as a preservative (eg, diazepam, phenytoin, lorazepam). Anion gap (lactic) metabolic acidosis, renal failure, hypotension	Hemodialysis Supportive care
Methemoglobinemia	Multiple causes including local anesthetics (eg, benzocaine spray administered by patient), dapsone, sulfonamides (trimethoprim-sulfamethoxazole), metoclopramide, rasburicase, nitrites/nitrates (eg, nitroglycerin, nitroprusside, nitric oxide)	Diagnosis with co-oximetry Methylene blue

Management of Common Intoxications: Common Medications

ACETAMINOPHEN

- Sx: Early, asymptomatic or nausea and vomiting; late, liver failure
- Dx: Serum acetaminophen level
- Tx: *N*-Acetylcysteine (NAC), liver transplantation

The majority of acetaminophen ingestion causes no significant clinical toxicity, but life-threatening liver injury and death can occur with overdose. Acute ingestions of 150 mg/kg (or 10 g) or the chronic ingestion in excess of 4 g/d may result in clinical toxicity. The generation of a toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), by the cytochrome P450 mixed function oxidase system (specifically the CYP2E1 enzyme) in the setting of overwhelmed hepatic glutathione results in hepatic and renal injury. Induction of CYP2E1 (eg, by ethanol, rifampin, isoniazid, or carbamazepine) or

decreased glutathione stores, as occurs with chronic malnutrition from alcoholism, increases the risk for acetaminophen toxicity.

The clinical signs and symptoms depend on the time of presentation and the amount of acetaminophen taken. Early on patients are asymptomatic, but they may develop anorexia, nausea, or vomiting. Liver injury usually occurs within 24 to 36 hours of ingestion as evidenced by elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and coagulation tests. Maximal hepatotoxicity is usually seen 72 to 96 hours after ingestion and may result in encephalopathy, coagulopathy, renal failure, hypoglycemia, and shock. Elevations in pancreatic enzymes and acute myocardial injury are also described.

In all cases of known or potential acetaminophen overdose, the serum level of acetaminophen should be measured at 4 hours after ingestion or as soon as possible thereafter and then plotted against time using the Rumack-Matthew nomogram (Figure 36.1). If an exact time of ingestion cannot be obtained, it is assumed to be the earliest possible time of ingestion. Plasma concentrations above the lower line (“possible risk”) are an indication for treatment with NAC (>150 mcg/mL if measured at 4 hours). Administration of NAC should not be delayed if serum level will not be available within 8 hours of ingestion or in cases of hepatotoxicity.

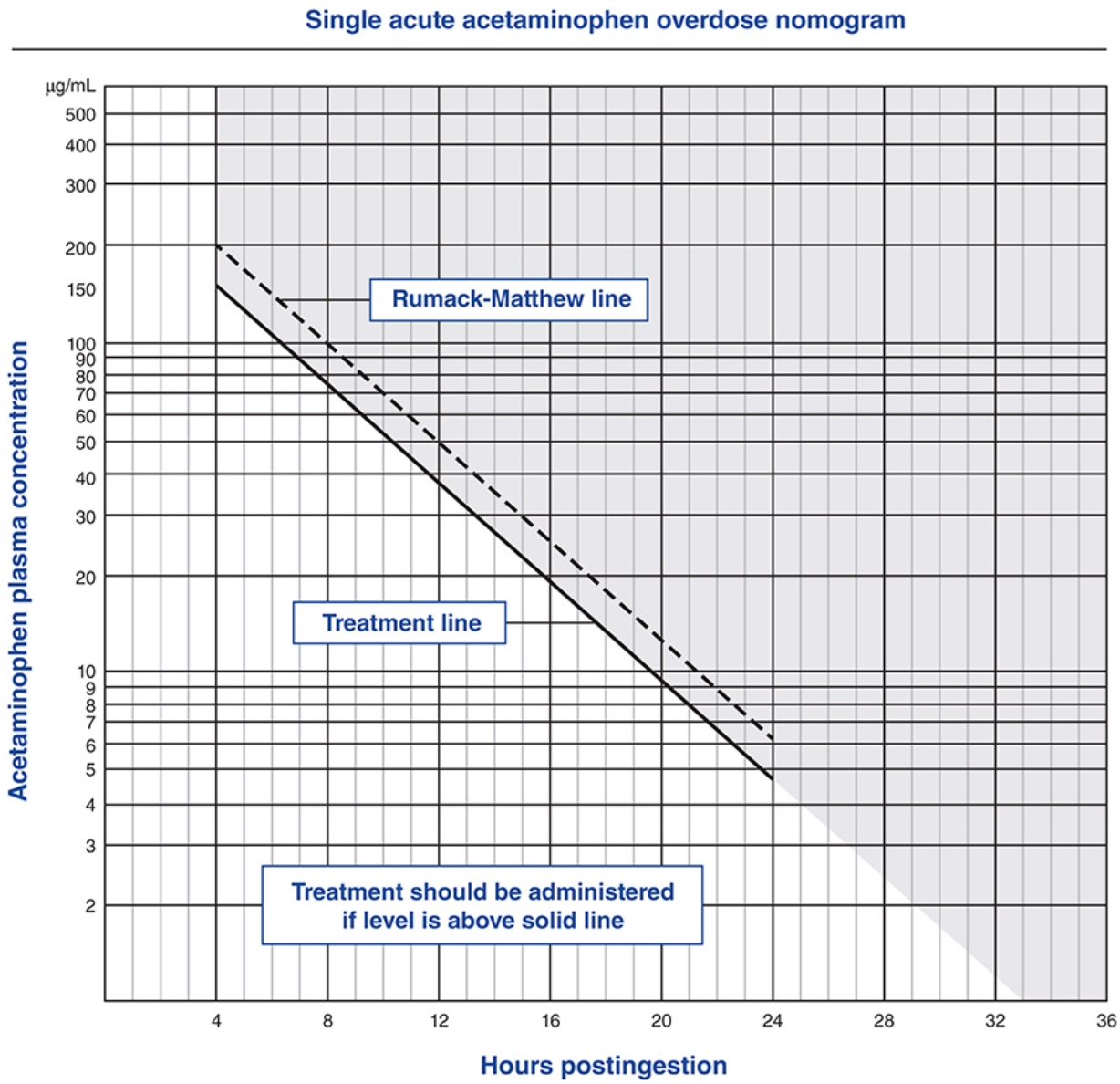


FIGURE 36.1 **Rumack-Matthew nomogram:** Plot of serial concentrations of acetaminophen versus time since acute ingestion to prognosticate liver toxicity. The nomogram is used to aid treatment decisions—when to start N-acetylcysteine—in the setting of acute acetaminophen overdose. (From Zipursky JS, Juurlink DN. Drugs and antidotes. In: Koyner JL, Topf J, Lerma E. *Handbook of Critical Care Nephrology*. Wolters Kluwer; 2022:292-308. Figure 27.2 and derived from Rumack BH , Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics*. 1975;55(6):871-876.)

NAC enhances both the synthesis of glutathione (which acts as an antioxidant) as well as the conversion of acetaminophen to (nontoxic) acetaminophen sulfate, rather than NAPQI. Several different NAC protocols have been used and are likely of similar efficacy (Table 36.11).

TABLE 36.11 *N*-Acetylcysteine Protocols for the Treatment of Acetaminophen Toxicity

20-h intravenous (IV) regimen as a continuous infusion (preferred protocol)	150 mg/kg IV given over 15 min, then 50 mg/kg IV given over 4 h, then 100 mg/kg IV given over 20 h
72-h oral (po) regimen	140 mg/kg po once, then 70 mg/kg po every 4 h × 17 doses

Prior to discontinuation of *N*-acetylcysteine, AST (aspartate aminotransferase) and acetaminophen levels should be measured to guide decisions regarding discontinuation or extension of treatment.
Continued administration should be considered in hepatic injury, persistent measurable acetaminophen level, PT/INR (prothrombin time/international normalized ratio) twice the upper limit of normal, or in hepatic encephalopathy. Consider hemodialysis or higher doses of *N*-acetylcysteine in discussion with an expert if persistent significantly elevated levels of acetaminophen are identified.

Although the nomogram assesses risk of toxicity with levels obtained from 4 to 24 hours postingestion, a pitfall of acetaminophen overdose management arises in patients with chronic ingestions or an unknown time of ingestion because they cannot be plotted on the Rumack-Matthew nomogram. Considering the relatively safe profile of NAC therapy and the disastrous consequences of failing to treat acetaminophen toxicity, early NAC treatment is recommended. Any patient with a suspected toxic acetaminophen ingestion with an unknown time of ingestion or ingestion beyond 24 hours should

continue treatment if either: (a) the presenting acetaminophen level is detectable (even if below the nomogram treatment line) or (b) the serum hepatic transaminases (eg, AST) measurements are elevated. In general, discontinuation of NAC therapy is appropriate in communication with a medical toxicologist either after a complete treatment course, normalization of serum transaminases, or clarification of the patient's ingestion history.

NAC therapy is available in both IV and oral formulations. Although neither has superior efficacy, most centers use the IV formulation for simplicity of administration. In general, NAC therapy is continued for the duration of therapy (20 hours for IV, 72 hours for oral), except in cases of hepatic injury, persistent measurable acetaminophen level, prothrombin time/international normalized ratio (PT/INR) twice the upper limit of normal, or in the presence of hepatic encephalopathy when longer treatment is usually recommended. Severe acetaminophen toxicity resulting in fulminant hepatic failure should be managed with early hepatology consultation or transfer to a tertiary center capable of liver transplantation. A suspected suicide attempt and drug or ethanol abuse alone may not preclude transplantation, but formal psychiatric assessment may be required. The most often used predictor of the need for liver transplantation after acetaminophen overdose is the King's College Hospital criteria: (a) pH less than 7.30 despite adequate fluid resuscitation or (b) the combination of grade III to IV hepatic encephalopathy, serum creatinine level greater than 3.4 mg/dL, and PT more than 100 seconds (INR >6.5). Serum lactate is an additional helpful prognostic marker. Acute renal failure is common in the setting of acetaminophen-induced fulminant hepatic failure and is likely multifactorial in nature. Intravascular volume status should be assessed.

SALICYLATES

- Sx: Tinnitus, vertigo, nausea and vomiting, confusion, hyperthermia, respiratory alkalosis, anion gap acidosis

- Dx: Salicylate level
- Tx: Alkalinization of the urine, hemodialysis

Salicylate toxicity results from both direct corrosive injury to the GI tract and multiple metabolic effects (eg, respiratory stimulation, uncoupling of mitochondrial oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and enhanced lipolysis with ketone generation). In addition to aspirin, salicylate may be included in preparations for cold or GI symptoms and is highly concentrated in oil of wintergreen. Patients may present with GI symptoms (eg, nausea, vomiting, and GI bleeding), diaphoresis, hyperthermia, tachycardia, ventricular arrhythmias, acute lung injury with pulmonary edema, and central nervous system (CNS) symptoms (eg, tinnitus, confusion, seizures, and coma). Laboratory studies will commonly show respiratory alkalosis with anion gap metabolic acidosis, deranged glucose regulation, prolonged PT, rhabdomyolysis, and renal failure. The clinical course may be dynamic. The finding of coincident CNS changes with tachycardia and diaphoresis suggests severe toxicity and warrants immediate, aggressive action. Many salicylate overdoses are accidental, so laboratory screening should be performed on any patient with an uncertain diagnosis who has nonspecific symptoms and a significant anion gap metabolic acidemia.

The diagnosis of salicylate exposure can be confirmed by obtaining a serum salicylate level. Activated charcoal may be administered for suspected or confirmed salicylate poisonings, and MDAC may be considered unless a contraindication exists (Table 36.5). Treatment consists of serum and urine alkalinization with IV sodium bicarbonate to enhance elimination and limit tissue redistribution. Dosing, goals, and monitoring parameters for serum and urine alkalinization are provided in Table 36.7. Hemodialysis should be considered in all clinically significant salicylate toxicity and is indicated in severe intoxications (Table 36.8). Delays in initiating hemodialysis when indicated may result in unnecessary morbidity and mortality. Serum glucose should be measured and dextrose is given empirically if confusion or seizures occur, as cerebral glucose

concentration may be decreased despite normal serum glucose concentrations. Benzodiazepines should be administered for seizures. Fluid deficits from vomiting and insensible losses may be substantial and should be treated with IV fluid.

BETA-BLOCKERS AND CALCIUM CHANNEL BLOCKERS

- Sx: Bradyarrhythmias, hypotension, atrioventricular (AV) blockade
- Dx: Clinical diagnosis
- Tx: Atropine, IV fluids, IV calcium, glucagon, high-dose insulin, vasopressors, extracorporeal life support

Beta-adrenergic receptor and calcium channel antagonists can result in significant toxicity, particularly in patients with underlying cardiovascular disease or when they are coingested. Clinical manifestations of toxicity are shared and primarily cardiovascular, causing bradyarrhythmias, hypotension, and cardiogenic shock. The diagnosis is made clinically, based on a typical presentation with a history of ingestion. The treatment strategy is similar; however, the two overdoses may be differentiated by serum glucose level and the presence of CNS toxicity. Beta-blockers may cause hypoglycemia due to the inhibition of gluconeogenesis and glycogenolysis. Conversely, calcium channel blockers tend to cause hyperglycemia due to the blockade of Ca^{2+} channels in the pancreas, decreasing insulin release. In the absence of shock, calcium channel blockers will rarely cause altered mentation. Agents within each class with unique pharmacologic properties may slightly influence the clinical presentation. More lipid-soluble beta-blockers (eg, propranolol, metoprolol, timolol) may cause CNS toxicity including confusion, seizures, and coma. Sotalol and acebutolol are unique beta-blockers with potassium channel blocking effects, which may cause prolonged QT interval and ventricular arrhythmias including ventricular tachycardia and torsade des pointes. Dihydropyridine-type calcium channel blockers (eg, amlodipine) may result in hypotension with reflex tachycardia due to a lack of activity on the sinoatrial and atrioventricular nodes, but this selectively can be lost at toxic doses

resulting in bradycardia. Sustained-release formulations may result in prolonged and/or delayed toxicity.

Initial treatment includes atropine and IV fluid boluses, but this is rarely sufficient to correct hypotension or bradycardia. Continued bradycardia and hypotension may be treated with IV calcium. A typical dose is 10 mL of 10% $CaCl_2$ (1 g) given over 2 to 3 minutes, with additional doses every 5 to 10 minutes for ongoing instability, followed by continuous infusion of 10% $CaCl_2$ at 10 mL/h. Glucagon should also be considered in these cases, starting with a 5 to 10 mg IV bolus, followed by continuous infusion at 1 to 10 mg/h. Glucagon provides sympathomimetic effects independent of blocked calcium channels or beta-adrenergic receptors. Further treatment of toxicity includes cardiac inotropy provided by high-dose insulin euglycemic therapy (1 unit/kg of regular insulin IV bolus followed by 0.5-10 units/kg/h IV infusion) with supplemental administration of dextrose for maintenance of euglycemia. Patients not responding to the above therapies may require the addition of inotropes (eg, dobutamine, epinephrine) or vasopressors (eg, norepinephrine, vasopressin). Inotropes or vasopressors may be ineffective at usual therapeutic doses and there is limited evidence available to recommend a specific inotrope or vasopressor. Therefore, agent choice should be driven by an assessment of the patient's hemodynamics and may require the use of invasive hemodynamic monitoring. Ventricular pacing can be considered, but many patients will have failure to capture, and increases in heart rate may not resolve hypotension. Extracorporeal life support should be considered in refractory cases. IV lipid emulsion may be considered in cases where extracorporeal life support is not available, and the patient continues to have hemodynamic instability despite the above treatments.

Severe toxicity from water-soluble beta-blockers such as acebutolol, nadolol, atenolol, and sotalol may be considered for extracorporeal removal, particularly in patients with renal failure (Table 36.8). Most calcium channel blockers are highly protein-bound with large volumes of distribution, making them less accessible to clearance by extracorporeal techniques.

DIGOXIN AND CARDIAC GLYCOSIDES

- Sx: Nausea, vomiting, altered mental status, visual disturbances, arrhythmias
- Dx: Serum digoxin level
- Tx: Digoxin-specific antibody (Fab) fragments

Digoxin and related cardiac glycosides (eg, plants foxglove, oleander) reversibly inhibit sodium-potassium ATPase, causing an increase in intracellular sodium and a decrease in intracellular potassium. Digoxin toxicity may occur from acute or chronic ingestion owing to a narrow therapeutic window. Changes in volume of distribution, diminished protein binding from hypoalbuminemia, and renal impairment can result in decreased elimination and increased risk for toxicity. Clinical features of toxicity include anorexia, nausea, vomiting, abdominal pain, and if severe, lethargy and delirium. Chronic toxicity tends to be more insidious and includes classic symptoms of blurred vision and altered color vision. Cardiac toxicity predisposing to arrhythmias is the most concerning effect. Digoxin toxicity may induce almost any cardiac arrhythmia including bradyarrhythmia, tachyarrhythmia, and AV blockade. Hypokalemia is more common with chronic ingestion, while hyperkalemia often occurs with acute toxicity and is correlated with increased mortality.

When digoxin toxicity is suspected, initial management includes acute stabilization, obtaining an ECG with continuous monitoring, and measuring serum electrolytes with a digoxin level. The normal therapeutic range for digoxin is 0.8 to 2.0 ng/mL. However, “toxic” levels have been described in asymptomatic patients, while toxicity has also been described in the setting of “normal” levels. Symptoms of severe intoxication (life-threatening arrhythmia, acute renal failure, altered mental status, or hyperkalemia >5.5 mEq/L) are indications for treatment with digoxin-specific antibody (Fab) (Table 36.2). Evidence to support the administration of Fab in patients without these symptoms is lacking, although some advocate its use when digoxin levels are greater than 10 ng/L in acute ingestions and

greater than 4 ng/mL in chronic ingestions based on the potential to develop symptoms. Hyperkalemia will typically correct shortly following administration of Fab; therefore, therapy for treatment of hyperkalemia should be viewed cautiously to avoid hypokalemia and its associated arrhythmias. Thus, aggressive treatment of hyperkalemia (eg, with bicarbonate, insulin, and glucose) is seldom warranted. Maintenance of normal serum levels of magnesium is also important. There is no proven beneficial role for hemodialysis. Digoxin is recirculated enterohepatically; therefore, MDAC should only be considered as a possible adjunctive therapy (Table 36.5).

NEUROLEPTIC MALIGNANT SYNDROME

- Sx: Autonomic instability, hyperthermia, altered mental status, lead pipe rigidity
- Dx: Clinical diagnosis
- Tx: Benzodiazepines, cooling, supportive care

Neuroleptic malignant syndrome (NMS) is an idiosyncratic response to a dopamine antagonist (eg, haloperidol, quetiapine, risperidone, olanzapine, metoclopramide) presenting as a constellation of symptoms featuring bradykinesia and rigidity. Symptoms typically begin to develop within 2 weeks after starting an antipsychotic. However, the development of NMS is unpredictable, and it can occur in patients with prolonged antipsychotic use at a stable dose or even following a single dose. Risk factors for development include recent or rapid increases in dose, addition of another antipsychotic, switching of agents, or parenteral administration. Sudden decreases in dopamine signaling within the CNS are thought to bring about the key features including thermodysregulation, dysautonomia, and muscular rigidity. Mental status changes can include agitation, catatonia, mutism, or coma. The diagnosis is made based on a history of exposure to a dopamine antagonist along with classic symptoms. Compared to serotonin syndrome, the onset of NMS is more gradual over days rather than hours, and the predominant feature is muscular rigidity rather than clonus and hyperreflexia, as

seen in serotonin syndrome. Creatine kinase is frequently elevated, and higher levels are tied to increased disease severity. Symptoms will typically persist for several days and may take up to 2 weeks to resolve.

Dopamine antagonists should be discontinued. Hyperthermia should be promptly and aggressively treated with the use of external cooling measures. Rhabdomyolysis may occur requiring fluid resuscitation. Benzodiazepines are first-line agents for the treatment of agitation, hyperthermia, or skeletal muscle hyperactivity. Patients with continued rigidity after benzodiazepines or with evidence of rhabdomyolysis should be considered for adjunctive therapies including dantrolene and/or bromocriptine. Dantrolene modulates skeletal muscle calcium release and has been successfully used in some cases of NMS. Typical dosing of dantrolene is 1.0 to 2.5 mg/kg IV followed by repeat doses of 1 mg/kg every 6 hours. Bromocriptine is a dopamine agonist that has also been used to treat NMS; a typical regimen starts at 2.5 mg PO/PT every 6 to 8 hours. Patients with refractory hyperthermia, compromised airway protection, or with respiratory failure may require intubation with nondepolarizing neuromuscular blockade.

SEROTONIN SYNDROME

- Sx: Autonomic instability, hyperthermia, altered mental status, hyperreflexia, clonus
- Dx: Clinical diagnosis
- Tx: Benzodiazepines, cooling, supportive care

Serotonin syndrome is a toxicity that can develop after exposure to a combination of serotonergic substances or after supratherapeutic or toxic ingestion of a single agent. Serotonergic substances may induce toxicity by inhibiting serotonin reuptake (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]), enhancing release (eg, amphetamines, cocaine), or by blocking metabolism (eg, monoamine oxidase inhibitors [MAOIs], linezolid). It is believed that increased serotonin

stimulation brings about the manifestations of toxicity including hyperthermia, altered mental status, nausea, vomiting, autonomic instability, tremor, diaphoresis, mydriasis, increased muscle tone, seizures, hyperreflexia, and clonus. Diagnosis is clinical, based on the history of exposure to a serotonergic agent and classic features. However, the Hunter Serotonin Toxicity Criteria may be used to assist with the diagnosis of serotonin syndrome. Criteria are met if any of the following three features are present:

1. Isolated spontaneous clonus
2. Tremor with hyperreflexia
3. Inducible or ocular clonus with any one of the following:
    a. Agitation
    b. Diaphoresis
    c. Hypertonicity plus hyperthermia (>38 °C)

Treatment priorities for patients with serotonin syndrome are discontinuing serotonergic medications, decreasing muscular activity, and reducing elevated temperature. Hyperthermia will cause progressive acidosis, rhabdomyolysis, disseminated intravascular coagulation, and multiorgan failure if left untreated. Reduction of hyperthermia may be achieved via external cooling measures and the administration of benzodiazepines. Benzodiazepines have been shown to decrease mortality in animal models and can decrease agitation, shivering, and excessive motor activity which will help to reduce body temperature. Physical restraints should be avoided as they can contribute to isometric muscle activity and further hyperthermia. Cyproheptadine is an antihistamine and nonspecific serotonin antagonist that should be considered for patients who do not show improvement after supportive measures and benzodiazepines. There is limited data to support cyproheptadine's efficacy, and it has anticholinergic effects that may cause further sedation and hypotension; therefore, it is not recommended for use as a first-line agent. Patients with a temperature greater than 41.1 °C or refractory to initial cooling measures may need to be sedated and

intubated with the use of a nondepolarizing neuromuscular blocking agent. After intubation and achievement of adequate sedation, paralytic agents should be considered.

TRICYCLIC ANTIDEPRESSANTS

- Sx: Anticholinergic toxidrome including tachycardia, confusion, seizures
- Dx: Clinical with abnormal ECG and TCA use history
- Tx: IV sodium bicarbonate

Although the use of TCAs for the treatment of psychiatric diseases has declined in recent years, drugs in this class are increasingly used as a treatment for chronic pain or insomnia. TCA overdose can result in life-threatening cardiovascular and CNS effects due to the narrow therapeutic window for these agents. Toxicity may vary with the class of TCA, but amitriptyline is particularly toxic. Drugs with similar toxicities include some antipsychotics. Symptoms from TCA toxicity are a result of anticholinergic effects, alpha-adrenergic blockade, inhibition of norepinephrine and serotonin reuptake, and blockade of the fast sodium channels in myocardium. Cardiotoxicity may manifest with tachycardia; prolongation of the PR, QRS, or QT intervals (quinidine-like effect); atrioventricular block; arrhythmias; depressed myocardial contractility; or hypotension. Seizures can occur, leading to acidosis, which may precipitate arrhythmias and hemodynamic collapse. Therefore, seizures should be treated promptly with benzodiazepines. Seizures when coupled with impaired sweating can also lead to life-threatening hyperthermia.

TCA overdose should be considered in any patient with an anticholinergic toxidrome, confusion, or coma, especially if accompanied by tachycardia, QRS prolongation, rightward axis deviation of the terminal 40 ms of the QRS complex, or QT interval prolongation. Specific drug levels are neither valuable nor required to make the diagnosis of acute intoxication. Qualitative urine and serum screens can retrospectively support the diagnosis of intoxication.

Initial management of TCA overdose is directed at emergent management of airway compromise, hemodynamic instability, cardiotoxicity, and seizures. Sodium bicarbonate should be given as an antidote for cardiotoxicity in the setting of ventricular arrhythmias, QRS prolongation greater than 100 ms, or in the presence of hypotension with acidosis (pH <7.20). A typical regimen would be 1 to 2 mEq/kg boluses every 3 to 5 minutes, until resolution of ECG changes or hypotension, with a target pH less than or equal to 7.55. This can be followed by an infusion of 150 mEq in 1 L of D5W at twice the maintenance fluid rate, adjusted to a target arterial pH of 7.45 to 7.50. The benefits of sodium bicarbonate therapy are multifactorial, including a favorable effect on myocardial sodium channels. Combination therapy with bicarbonate infusion and hyperventilation should be avoided because of the risk of induction of a life-threatening alkalosis and hypokalemia.

Lidocaine (Class IB) may be considered in cases refractory to serum alkalinization with sodium bicarbonate. Class 1A and 1C antiarrhythmics (eg, procainamide and flecainide) should be avoided in the management of arrhythmias. Although the evidence is limited, magnesium sulfate has been shown to be effective for TCA-induced wide complex tachycardia unresponsive to other agents. Benzodiazepines should be used to treat TCA-induced seizures, with propofol used for refractory cases. Activated charcoal should be given if no contraindication exists in patients presenting within 2 hours of ingestion. Infusion of lipid emulsion (20%) may be used (1.5 mL/kg over 1 minute, followed by an infusion of 0.25-5 mL/kg/h) in unstable patients, refractory to standard treatment. Hemodialysis and hemoperfusion are not shown to be beneficial in TCA overdose. Physostigmine should not be given in the management of TCA overdose because of the significant toxicity associated with use.

Drugs of Abuse

ALCOHOLS

- Sx: Sedative-hypnotic toxidrome, all alcohols present similarly with ataxia, dysarthria, somnolence, respiratory depression, odor on breath
- Dx: Elevated serum alcohol levels, elevated osmolal gap, elevated anion gap (methanol, ethylene glycol)
- Tx: Fomepizole

Ethanol is widely abused and is a common component of mixed ingestions, particularly in suicide attempts. Toxicity may present with ataxia, dysarthria, CNS depression, and respiratory depression. The diagnosis should be suspected based on the presence of symptoms in the patient with characteristic ethanol odor and can be confirmed by measuring the blood ethanol level. Elevated levels are of greater concern in the naïve user compared to chronic user and must be interpreted relative to time of ingestion. Treatment is largely supportive and directed at ensuring a patent airway and ventilation. Three toxic alcohol ingestions are important to diagnose quickly in critically ill patients: isopropanol, methanol, and ethylene glycol. The key to diagnosis for these ingestions is maintaining a high index of suspicion and measuring the anion and osmolal gaps.

Isopropanol is a component of rubbing alcohol and other household compounds that may be intentionally ingested as an alternative to ethanol. Clinical manifestations include GI irritation, upper GI bleeding, CNS depression, and respiratory depression. Diagnosis should be considered in patients with these symptoms, particularly when presenting with fruity breath (due to acetone production), ketosis, and an elevated serum osmolal gap. Isopropanol toxicity is differentiated from the other alcohols by the lack of an anion gap metabolic acidosis. The diagnosis can be confirmed by measuring the serum level. As with ethanol intoxication, treatment is largely supportive. Patients in a state of confusion or coma should be screened for hypoglycemia and treated with thiamine, 500 mg followed by 25 g dextrose, IV. Isopropanol may be removed by hemodialysis, but this is rarely necessary. Upper GI bleeding should be managed with standard therapies.

Methanol is found in many household solvents and may be ingested as a substitute for ethanol. It may also be found in homemade spirits and ingested unknowingly. Patients initially present with inebriation. After a characteristic latent period of 12 or more hours, severe manifestations of toxicity including anion gap acidosis, visual disturbance, blindness, respiratory failure, seizures, and coma may occur. Physical examination should include assessment of the pupillary light reflex and funduscopic exam to assess optic nerve injury and vision. Methanol ingestion should be considered in all cases of elevated anion gap. The screening test of choice is the osmolal gap. Definitive diagnosis may be made by measuring the serum methanol level, although later presentations may reveal undetectable methanol levels (but elevated formate levels). Toxicity results when methanol is converted to formaldehyde and then to formate by alcohol dehydrogenase. Fomepizole should be given as a competitive inhibitor of alcohol dehydrogenase in cases of methanol levels greater than 20 mg/dL, acidemia, or an elevated osmolal gap. Fomepizole is dosed at 15 mg/kg IV over 30 minutes, followed by 10 mg/kg IV every 12 hours for four doses, followed by 15 mg/kg IV every 12 hours as needed until the serum methanol level is less than 20 mg/dL. Folic acid 50 mg IV every 6 hours should be given to promote conversion of formate to CO_2 and water. Ethanol as a treatment is a less effective and more toxic inhibitor of alcohol dehydrogenase. Hemodialysis may be beneficial, and indications are in Table 36.8. Treatment with fomepizole and hemodialysis should be initiated rapidly without waiting for definitive measurement of a methanol level.

Ethylene glycol is found in antifreeze and may be ingested during suicide attempts or as a substitute for ethanol. Early toxicity manifests with CNS depression. As with methanol, delayed toxic manifestations (after 4-12 hours) are often more severe and may include metabolic acidosis, renal failure, seizures, coma, and death. Toxicity arises from the formation of toxic metabolites (glycolaldehyde and oxalate) generated by alcohol dehydrogenase. Ethylene glycol should be considered in all cases of elevated anion

gap and elevated osmolal gap. Diagnosis can be confirmed by measuring the serum level, but treatment should not be delayed if clinical suspicion of ingestion is high. Indications for therapy include a serum ethylene glycol level greater than 20 mg/dL, the presence of acidosis, or an elevated osmolal gap. Dosing and administration of fomepizole is the same as described for methanol poisoning. Fomepizole should be continued until the serum level of ethylene glycol is less than 20 mg/dL. Thiamine (100 mg IV) and pyridoxine (100 mg IV) supplementation may promote metabolism of ethylene glycol. Hemodialysis may be beneficial and indications are in Table 36.8.

OPIOIDS

- Sx: Opioid toxidrome including lethargy, hypercarbic respiratory failure, miosis
- Dx: Clinical diagnosis
- Tx: Naloxone, mechanical ventilation

Opioid-intoxicated patients typically present with lethargy, miosis, decreased GI motility, and respiratory depression ranging from hypoventilation to apnea. ABG analysis may reveal an elevated $Paco_2$ and hypoxemia in severe intoxication. Hypotension (resulting from histamine release) is more common with certain agents (eg, meperidine). Noncardiogenic pulmonary edema may occur. Seizures may occur as a result of the accumulation of neurotoxic metabolites of certain opioids (specifically meperidine, propoxyphene, and tramadol). Acetaminophen or aspirin toxicity may complicate the patient's presentation and management when combination analgesics have been ingested. Drug screens may not detect some opiate medications (eg, fentanyl, methadone). As such, patients with a toxidrome consistent with opioid toxicity should be treated empirically regardless of toxicology screening tests.

Management of opioid intoxication is primarily directed at ensuring airway protection and ventilation through the early use of the opioid

antagonist naloxone. Naloxone may be given intranasal, IM, or IV. Naloxone is given initially at doses of 0.04 to 2.0 mg IV every 2 minutes until effect to a maximum of 10 mg. The desired effect is the maintenance of airway protection and adequate ventilation. Naloxone doses above this target effect may precipitate withdrawal, agitation, and pain. Naloxone should be viewed as an agent to prevent intubation, not for use after mechanical ventilation is initiated. The duration of naloxone action is 1 to 2 hours, which may be shorter than the activity of the opioid intoxicant, mandating patient monitoring for several hours (Table 36.12). Intoxication with long-acting opioids may require repeated doses of naloxone. Continuous naloxone infusions can be used at two-thirds of the original response dose per hour (dosing assistance from a pharmacist or toxicologist is recommended). In patients with significant intoxication, it may be prudent to support patients with mechanical ventilation while intoxicated rather than attempt to re-dose naloxone. Body packers should be treated with activated charcoal, WBI, and naloxone infusion if symptomatic.

TABLE 36.12 Half-Life of Selected Opioids

Opioid	Half-Life
Codeine	3 h
Fentanyl	2-4 h (intravenous) 3-14 h (transdermal) 3-14 h (transmucosal) 15-25 h (nasal spray)
Heroin	2-6 min, metabolized to monoacetylmorphine in 2-6 min, then to morphine
Hydrocodone	3-4.5 h
Hydromorphone	2-3 h (immediate release) 11 h (extended release)

Opioid	Half-Life
Methadone	8-59 h
Meperidine	2-4 h Active metabolite 15-30 h or longer with renal failure
Morphine	2-4 h (immediate release) 11-24 h (extended release)
Opium tincture	36 h
Oxycodone	2-4 h
Oxymorphone	7-9 h (immediate release) 9-11 h (extended release)
Tramadol	4-6 h

COCAINE AND AMPHETAMINE-RELATED TOXINS

- Sx: Sympathomimetic toxidrome
- Dx: Clinical history, urine drug screen
- Tx: Benzodiazepines and antihypertensives (except beta-blockers)

Cocaine intoxication can result in life-threatening cardiovascular, pulmonary, and CNS complications. Mechanisms of toxicity include inhibited monoamine reuptake and enhanced catecholamine release (together resulting in increased levels of catecholamines), as well as blockade of Na^+ channel activity. In addition, cocaine promotes thrombogenesis and vasoconstriction. Cocaine intoxication mimics features of amphetamine, methamphetamine, synthetic cathinone ("bath salts"), 3,4-methylenedioxymethamphetamine (MDMA), and synthetic cannabinoid toxicity, and has shared management strategies. The clinical presentations of cocaine intoxication and other sympathomimetics may be quite varied. Hyperthermia, hypertension, and tachycardia are common. Neuropsychiatric

presentations may include agitation, confusion (“excited delirium”), dystonic reactions, cerebrovascular thrombosis, intracranial hemorrhage, and seizures. Cardiovascular complications include acute myocardial infarction and arrhythmias. Pulmonary complications of cocaine use may include barotrauma (eg, pneumothorax, pneumomediastinum) from coughing or intranasally inhaling cocaine, pulmonary edema (cardiogenic or noncardiogenic), alveolar hemorrhage, and inhalational heat or burn injury to the aerodigestive tract mucosa. Vasoconstriction can cause intestinal, hepatic, or renal ischemia. Rhabdomyolysis is common in those with psychomotor agitation. Cocaine or amphetamine use during pregnancy may result in fetal toxicity, abruptio placentae, spontaneous abortion, and premature labor.

Urine drug screens may be positive for cocaine for 2 to 3 days after use and false-negative test results can occur. Markers for cardiac injury, creatinine phosphokinase levels, and urinalysis should be obtained in patients with significant intoxication.

Management of cocaine toxicity depends on the presentation. Benzodiazepines (eg, diazepam 5-10 mg every 5 minutes as needed) function as first-line therapy for agitation and most manifestations of toxicity. If seizures are present, IV lorazepam is recommended. Treatment of hyperthermia includes adequate sedation and, if necessary, external cooling. Hypertension is best treated with sedation first, and if necessary, calcium channel blockers (eg, titrated clevidipine or nicardipine infusion), sodium nitroprusside, or phentolamine. Pure beta-blockers are contraindicated. Other contraindicated medications are listed in Table 36.13.

TABLE 36.13 Medications Contraindicated and Recommended in Cocaine Intoxications

Contraindicated Drug Treatment	Complication of Use	Recommended Alternatives

Contraindicated Drug Treatment	Complication of Use	Recommended Alternatives
Pure beta-blockers	Unopposed alpha-adrenergic activity may cause hypertension or coronary vasospasm.	For hypertension and supraventricular tachycardia: calcium channel blockers
Phenothiazines and butyrophenone antipsychotics (eg, droperidol, prochlorperazine, haldol)	Increase seizure risk, prolong QT interval, promote dystonic reactions	For agitation: benzodiazepine, dexmedetomidine
Succinylcholine	Exacerbation of rhabdomyolysis-induced hyperkalemia, prolonged toxicity, or paralysis	For paralysis: nondepolarizing paralytics (eg, rocuronium)
Class IA & IC antiarrhythmics (eg, procainamide)	Increased QRS and QT prolongation and potentiate cocaine effects	For ventricular arrhythmias: IV sodium bicarbonate, lidocaine, IV magnesium

IV, intravenous.

Chest pain should be thoroughly evaluated. Possible causes include acute coronary events, aortic dissection, and pneumothorax. Cocaine may impair the coronary artery perfusion by vasoconstriction via alpha-adrenergic stimulation, prothrombotic effects via thromboxane, and promotion of atherosclerosis in chronic use. Cardiac ischemia occurs in at least 5% of those with cocaine use presenting to the ED, so a high index of suspicion should prompt the use of aspirin, nitroglycerin, and benzodiazepines. An ECG and serial troponin measurements should be obtained.

Supraventricular arrhythmias are treated with calcium channel blockers (eg, diltiazem) as pure beta-blockers are contraindicated. Ventricular arrhythmias should be treated with benzodiazepines, control of ischemia, correction of electrolytes, and if necessary,

lidocaine. Class IA antiarrhythmics (eg, procainamide) should be avoided. The use of amiodarone for ventricular arrhythmias is not studied in humans. Management of body packing by drug smugglers may include activated charcoal and WBI if asymptomatic, but immediate surgical removal is required in patients with any signs of cocaine intoxication, suggesting packet rupture. Attempts to retrieve drug packets by endoscopy risk drug spillage and are not recommended, particularly in the asymptomatic patient.

SYNTHETIC CANNABINOIDS

- Sx: Variable, sympathomimetic toxidrome
- Dx: Clinical history and symptoms
- Tx: Supportive, benzodiazepines

Cannabinoids (ie, K2, “Spice,” synthetic marijuana) are increasingly popular in the United States. These agents bind to the cannabinoid receptors in the brain and spinal cord. Synthetic cannabinoids are not detected on standard urine drug screens, so the diagnosis is clinical. Patients typically will present with tachycardia, agitation, and vomiting. Those with severe symptoms may present with hyperthermia, seizures, psychosis, cardiac ischemia, or renal failure (with rhabdomyolysis) resulting in metabolic derangements. Management is supportive, as determined by the clinical features. Acute agitation should be treated with benzodiazepines, using repeat doses as needed. Antipyretic agents are not effective, but fluids should be repleted and electrolytes closely monitored.

Environmental Exposures

CARBON MONOXIDE

- Sx: Nausea and vomiting, headache, lethargy, confusion
- Dx: Exposure history, oxygen saturation gap, elevated COHb

- Tx: 100% oxygen, hyperbaric oxygen (HBO_2) when indicated

CO competes with O_2 for hemoglobin-binding sites (forming COHb) and has an affinity for hemoglobin that is greater than 200 times that of O_2. COHb dissociates extremely slowly, resulting in inadequate oxygen delivery to peripheral tissues.

Symptoms are related to tissue hypoxia. Neurologic symptoms of toxicity include headache, confusion, vision changes, and coma. Nausea and vomiting are common. Cardiac manifestations include arrhythmias and myocardial ischemia or infarction. Less commonly, rhabdomyolysis, pancreatitis, and hepatic injury may be seen. Pulmonary edema may occur as a consequence of primary cardiac disturbance or from associated smoke inhalation. Delayed neurologic manifestations (eg, impaired concentration, amnesia, and depression) are common months later.

CO poisoning should be suspected after certain exposures (eg, smoke, poorly ventilated car exhaust, gas stoves, and space heaters). The diagnosis can be confirmed by analyzing arterial blood by co-oximetry, which will allow measurement of COHb. Symptoms and signs of CO toxicity may correlate poorly with the measured COHb levels. Oxyhemoglobin assessments by pulse oximetry (Spo_2) or by estimates made from the partial pressure of oxygen (as reported by some ABG analyzers) can be misleading in CO poisoning. A device for measuring COHb noninvasively using light transmitted through a capillary bed (similar to pulse oximetry) is available for screening but lacks accuracy, and laboratory co-oximetry confirmation is required.

The treatment of CO toxicity is 100% oxygen, with consideration of noninvasive positive pressure ventilation to promote gas delivery and clearance. The half-life of COHb varies inversely with the alveolar partial pressure of O_2. For this reason, HBO_2 therapy has been used to treat CO toxicity since the 1960s. The threshold indications to institute HBO_2 therapy are not well defined, but most experts recommend this therapy for patients who have had loss of consciousness, neurologic abnormalities, cardiac ischemia, or

pregnancy. There is a lower threshold for treatment of pregnant patients due to increased affinity of CO by fetal hemoglobin. The benefits of HBO_2 therapy are thought to be greatest when administered promptly (within 6 hours of exposure) to mitigate late neurologic sequelae.

SNAKE ENVENOMATION

- Sx: Pain and swelling, coagulopathy, renal failure, paralysis
- Dx: Clinical diagnosis
- Tx: Antivenom, supportive

Most snakes are nonvenomous, and often even venomous snake bites do not cause envenomation (“dry bites”). Venomous snakes are grouped into two families: Elapidae (eastern coral snake) and Viperidae (pit vipers: rattlesnake, water moccasin or cottonmouth, copperhead). In the United States, the vast majority of bites are from members of the Viperidae family with only 2% of reported bites attributable to Elapidae species.

Viperidae envenomation is typically characterized by local tissue and hematologic toxicity including rapidly increasing tissue swelling, ecchymosis, coagulopathy, rhabdomyolysis, hypotension, and nonspecific systemic symptoms (nausea, vomiting, diaphoresis, diarrhea, and weakness). Elapidae envenomation typically consists of moderate local effects with rapid onset neurotoxicity (ptosis, ophthalmoplegia, dysarthria, dysphagia, dysgeusia, fasciculations, paralysis, respiratory failure, and seizures).

Treatments that are no longer recommended include tourniquets, prophylactic antibiotics, prophylactic fasciotomy, pressure immobilization, and cutting or suctioning the wound. Approximately 70% of all reported snake bites in the United States receive antivenom therapy. Be aware that exotic collectors may have snakes that do not respond to Crotalidae antivenom, and specific antivenom treatment may be required.

Recommended treatment of North American snake envenomation includes IV access, laboratory testing (CBC [complete blood count], PT/PTT [prothrombin time/partial thromboplastin time], fibrinogen, electrolytes, renal, and hepatic profiles), analgesia, and clinical reevaluation every 15 minutes. The leading edge of edema should be marked. Antivenom poses a risk of anaphylaxis; therefore, it should not be administered prophylactically or in patients lacking signs of envenomation or systemic toxicity. In general, antivenom is indicated if the patient exhibits hematologic toxicity, neuromuscular toxicity, progressive edema, or hemodynamic instability. Starting doses vary with the clinical scenario and antivenom used; therefore, poison control or an expert should be contacted to help guide antivenom administration. Patients should be tested for reversal of coagulopathy 1 hour after antivenom administration. Redosing and maintenance dosing may be needed, according to the patient's response and antivenom formulation used, until control is obtained. Control is achieved with the arrest of progressive tissue edema, hemodynamic stability, resolution of systemic toxicity, and partial or complete reversal of coagulopathy. Upon discharge, patients should be scheduled for repeat testing of coagulation parameters and be advised of an increased bleeding risk for at least 2 weeks.

SUGGESTED READINGS

Armstrong J, Pascu O, eds. *The Toxicology Handbook*. 4th ed. Elsevier; 2022.

Concise bedside reference guide for the management of the poisoned patient.

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Brooks DE, Levine M, O'Connor AD, et al. Toxicology in the ICU: part 2: specific toxins. *Chest.* 2011;140(4):1072-1085.

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SECTION X INFECTIOUS DISEASES

37 Central Nervous System Infections

Marilia Rita Pinzone and M. Cristina Vazquez Guillamet

Central nervous system (CNS) infections are associated with significant morbidity and mortality, often requiring an intensive care unit (ICU) level of care. Up to 50% of patients with meningitis require intubation, usually because of altered mental status. Other complications that often lead to ICU admission include septic shock, management of increased intracranial pressure, and seizures.

Community-Acquired Central Nervous System Infections: Approach to the Patient With Suspected Meningitis or Encephalitis

Meningitis is the inflammation of the leptomeninges surrounding the brain and spinal cord, while encephalitis refers to the inflammation of the brain parenchyma.

Acute bacterial meningitis is a medical emergency that requires prompt diagnosis and initiation of antimicrobial treatment—ideally within 1 hour—to reduce the risk of long-term complications and death. As shown in Table 37.1, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the two most common microorganisms causing community-acquired meningitis. Individuals with impaired cell-mediated immunity, as well as older individuals, are at an increased risk for *Listeria* meningitis. Other host immune defects also increase the risk of meningitis due to specific etiologies. For instance, cryptococcal meningitis is commonly associated with untreated advanced human immunodeficiency virus (HIV) infection, but it can also affect immunocompetent individuals. Also, asplenia

increases the risk of invasive infections due to encapsulated bacteria such as *N. meningitidis* and *S. pneumoniae*. While community-acquired meningitis due to gram-negative bacteria is uncommon in immunocompetent individuals, it can be observed in older individuals and those with liver disease or diabetes. Gram-negative meningitis can be associated with hyperinfection syndrome due to strongyloidiasis in immunosuppressed individuals.

TABLE 37.1 Common Etiologies for Community-Acquired CNS Infections

	Etiology	Notes
Acute bacterial meningitis	*Streptococcus pneumoniae* *Neisseria meningitidis*	Consider *Listeria monocytogenes* and aerobic gram-negative bacilli if age >50 y, chronic steroid use, alcoholism, diabetes, malignancy
Viral meningitis	Enteroviruses[a] Arboviruses[a] HSV	Many pathogens can case aseptic meningitis, not only viruses (HIV, CMV, EBV, VZV, LCMV, HSV-1, HSV-2, measles, mumps), but also bacteria (*Treponema pallidum, Borrelia burgdorferi*), and fungi (*Cryptococcus* spp., *Coccidioides immitis*)
Encephalitis	HSV Enteroviruses[a] Arboviruses (including WNV)[a]	Broad differential in immunocompromised individuals: consider VZV, CMV, WNV, HHV-6, HIV, JC virus, *L. monocytogenes, Cryptococcus neoformans, C. immitis, Histoplasma capsulatum, Toxoplasma gondii* If exposure to ticks, consider *Ehrlichia* and *Anaplasma* spp., Powassan virus, *B. burgdorferi* depending on time of the year and geography If history of cat scratch, consider bartonellosis If history of bite injury (dogs, bats), consider rabies

CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV, herpes

simplex virus; JC virus, John Cunningham virus; LCMV, lymphocytic choriomeningitis virus; VZV, varicella zoster virus; WNV, West Nile virus.
[a]Summer and fall.

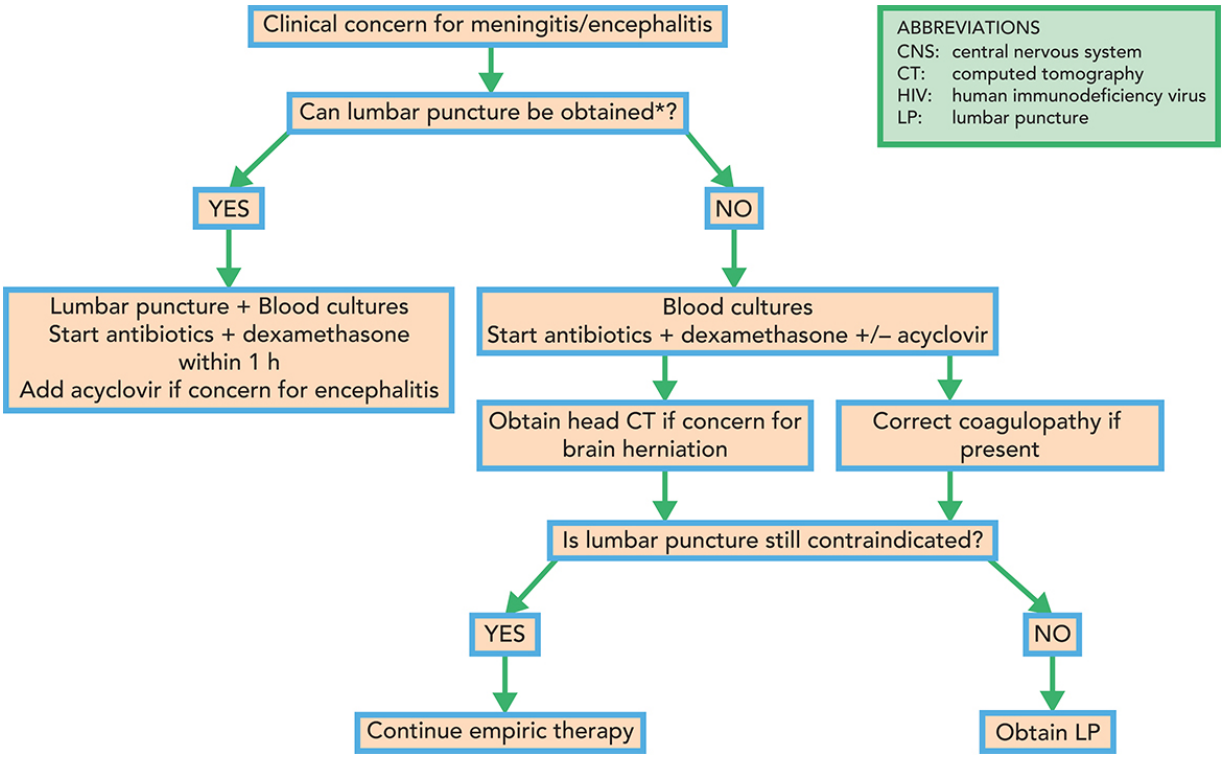
Typically, patients present with fever, nuchal rigidity, headache, and changes in mental status. Most patients have at least two of these symptoms. The absence of all these symptoms has a very high negative predictive value for acute bacterial meningitis. The acute onset and rapid clinical deterioration observed in acute bacterial meningitis contrast with a more subtle course observed in patients with aseptic meningitis. Aseptic meningitis usually has a viral (enteroviruses, arboviruses, herpes simplex virus [HSV]-2) or noninfectious etiology. The presence of a petechial rash might suggest meningococcal meningitis, while extra-meningeal foci of infection such as otitis, sinusitis, endocarditis, and pneumonia are commonly associated with streptococcal etiology.

A hallmark of encephalitis is the presence of altered mental status and focal findings, such as cranial nerve involvement or new generalized or partial seizures. Meningitis and encephalitis frequently overlap in clinical presentation, as both may affect the meninges and brain parenchyma (patients with *Listeria* meningitis can develop rhombencephalitis, presenting with ataxia, cranial nerve palsies, and nystagmus). HSV is the most common cause of encephalitis (Table 37.1) and the only viral etiology for which an effective treatment is available. Of note, a seasonal distribution in the summer and early fall may occur with West Nile virus (WNV) and enteroviruses. During the summer months, tick-borne diseases, such as ehrlichiosis and anaplasmosis, can also present with encephalitis. Host immune status can again provide helpful clues for other possible etiologies. In immunocompromised individuals, additional etiologies to consider include viruses (especially varicella zoster virus [VZV], cytomegalovirus [CMV], and John Cunningham [JC] virus), protozoa such as *Toxoplasma gondii*, and fungi (especially *Cryptococcus neoformans*) (Table 37.1). An HIV fourth-generation test should be obtained in every patient presenting with altered

mental status, as a positive result would dramatically change the differential and diagnostic work-up.

Delays in antibiotic therapy are associated with increased mortality; thus, every patient with a suspected CNS infection should receive prompt empiric antimicrobial therapy (Algorithm 37.1). Two sets of blood cultures should be obtained prior to antibiotic treatment. Up to 50% to 90% of patients with bacterial meningitis will have positive blood cultures, with a higher yield if collected before starting antibiotics. Analysis of the cerebrospinal fluid (CSF) is the most important diagnostic step (Table 37.2), and a lumbar puncture (LP) should be attempted whenever possible. However, there should be no delay in starting antimicrobial therapy if an LP is deferred or delayed. Some preexisting conditions necessitate head computed tomography (CT) imaging prior to LP, such as a history of CNS disease, a history of recent seizures, altered level of consciousness, new focal neurologic deficits on examination, papilledema, or neurologic findings in the setting of immunosuppression.

ALGORITHM 37.1 Patients With Suspected Meningitis or Encephalitis



*Possible contraindications include presence of coagulopathy, history of CNS disease, recent seizure, altered level of consciousness, new focal neurologic deficits, papilledema or neurologic findings in the setting of immunosuppression (for instance, HIV, solid organ or hematopoietic cell transplantation, immunosuppressive therapy).

TABLE 37.2 Typical Cerebrospinal Fluid Findings in Central Nervous System Infections

CSF Findings	Normal	Bacterial Meningitis	Viral Meningitis	Encephalitis
Opening pressure (cm H_2O)	10-20	Increased	Normal to mildly increased	Normal to mildly increased
WBC count/mcL	0-5	≥1,000 with neutrophil predominance	10-1,000 with lymphocyte predominance	10-500 with lymphocyte predominance

CSF Findings	Normal	Bacterial Meningitis	Viral Meningitis	Encephalitis
Protein (mg/dL)	15-40	Increased	Mildly increased	Mildly increased
CSF to serum glucose ratio	>0.6	≤0.4	Normal	Normal

CSF, cerebrospinal fluid; WBC, white blood cell.

Ideally, the opening pressure should be recorded, and the last tube of CSF should be sent for analysis, including glucose and protein concentration, cell count with differential, Gram stain, and bacterial culture. Additional tests may be required depending on the clinical presentation (cryptococcal antigen, HSV polymerase chain reaction [PCR], and WNV IgM). Gram stain can be positive in 50% to 90% of individuals with bacterial meningitis. The Food and Drug Administration (FDA) has approved a multiplex nucleic acid amplification test (NAAT), the FilmArray Meningitis/Encephalitis (ME) Panel, which includes 14 pathogens commonly associated with CNS infections, including several bacteria, viruses, and *C. neoformans* or *Cryptococcus gattii*). Fungal, viral, and acid-fast bacilli cultures may be low yield in the setting of acute meningitis or encephalitis. The laboratory can hold a quantity of CSF for additional testing following initial findings.

Acyclovir should be added to the antibiotic treatment in patients older than 50 years of age with symptoms of encephalitis. Tables 37.3 and 37.4 outline recommendations for empiric and targeted treatment regimens. Vancomycin provides coverage for penicillin-resistant pneumococci and can be discontinued after susceptibility results. Cefepime can be considered as an alternative to ceftriaxone if coverage for gram-negative bacteria, including *Pseudomonas aeruginosa,* is needed (for instance, in immunocompromised individuals with neutropenia or impaired

mucosal barriers or at risk for nosocomial meningitis). The use of adjuvant steroids in the treatment of bacterial meningitis remains controversial. A Cochrane meta-analysis did not find a mortality benefit. However, a subgroup analysis showed a decrease in mortality in patients with *S. pneumoniae* meningitis, as well as a decrease in hearing loss and short-term neurologic sequelae in *Haemophilus influenzae* meningitis. Currently, the Infectious Diseases Society of America (IDSA) guidelines recommend the administration of steroids to all patients with suspected or proven pneumococcal meningitis. Steroids should be stopped if other etiologies are identified (see Algorithm 37.1). The recommended antimicrobial treatment duration for CNS infections is summarized in Table 37.5.

TABLE 37.3 Empiric Treatment Recommendations for Central Nervous System Infections

Etiology	Suggested Therapy	Notes
Acute bacterial meningitis	Vancomycin 15-20 mg/kg[a] IV Q8H *plus* ceftriaxone 2 g IV Q12H	Add ampicillin 2 g[a] IV Q4H if ≥50 y or immunosuppressed host Add acyclovir 10 mg/kg[a] Q8H if concern for HSV meningoencephalitis Add dexamethasone 0.15 mg/kg Q6H for 4 d (start at the time of antibiotic initiation and continue if pneumococcal etiology is confirmed)
Health care–associated ventriculitis or meningitis	Vancomycin 15-20 mg/kg[a] IV Q8H *plus* cefepime 2 g[a] IV Q8H *or* Vancomycin *plus* meropenem 2 g[a] Q8H IV	Can consider linezolid 600 mg Q12H IV as alternative to vancomycin Meropenem provides empiric coverage for *Listeria*

Etiology	Suggested Therapy	Notes
Viral meningitis	Supportive care only	
HSV encephalitis	Acyclovir 10 mg/kg[a] Q8H IV	
If history of severe beta-lactam allergy	Vancomycin 15-20 mg/kg[a] IV Q8H *plus* moxifloxacin 400 mg IV Q24H	Add aztreonam 2 g[a] IV Q6H *or* ciprofloxacin 400 mg[a] IV Q8H if antipseudomonal coverage is required[b] Add trimethoprim-sulfamethoxazole 5 mg/kg[a] daily (based on trimethoprim component) if *Listeria* coverage is required

HSV, herpes simplex virus; IV, intravenous.

[a]Dose adjustment needed based on renal function.

[b]Aztreonam can cross-react with ceftazidime and should be avoided if there is a known history of severe allergy to either aztreonam or ceftazidime.
Derived from the Infectious Diseases Society of America (IDSA) and consensus guidelines.

TABLE 37.4 Treatment Recommendations for Selected Pathogens Responsible for Community-Acquired Meningitis

Etiology	Suggested Antibiotic Therapy
Streptococcus pneumoniae	If PCN MIC <0.1 mcg/mL, penicillin G 4 million units IV Q4H or ampicillin 2 g[a] IV Q4H If PCN MIC 0.1-1 mcg/mL, ceftriaxone 2 g IV Q12H If PCN MIC ≥2 mcg/mL, vancomycin 15-20 mg/kg[a] IV Q8H *plus* ceftriaxone 2 g IV Q12H
Neisseria meningitidis	If PCN MIC <0.1 mcg/mL, ampicillin 2 g[a] IV Q4H *or* penicillin G 4 million units IV Q4H If PCN MIC ≥0.1-1 mcg/mL, ceftriaxone 2 g IV Q12H

Etiology	Suggested Antibiotic Therapy
Listeria monocytogenes	Ampicillin 2 g[a] IV Q4H *or* penicillin G 2 g IV Q4H[b]
Haemophilus influenzae	If beta-lactamase negative, ampicillin 2 g[a] IV Q4H If beta-lactamase positive, ceftriaxone 2 g IV Q12H

HSV, herpes simplex virus; IV, intravenous; MIC, minimum inhibitory concentration; PCN, penicillin.

[a]Dose adjustment needed based on renal function.

[b]Consider adding gentamicin for synergy.
Derived from the Infectious Diseases Society of America (IDSA) and consensus guidelines.

TABLE 37.5 Suggested Length of Treatment for Central Nervous System Infections

Etiology	Length of Treatment (d)
Streptococcus pneumoniae	14
Neisseria meningitidis	7
Haemophilus influenzae	7
Listeria monocytogenes	≥21
Group B streptococci	14-21
Gram-negative bacilli	21
Herpes simplex virus	14-21

Derived from the Infectious Diseases Society of America (IDSA) and consensus guidelines.

Neisseria meningitidis and *H. influenzae* are spread via large particle droplets larger than 5 mcm in size. Infection with either of these organisms warrants droplet precautions for the first 24 hours of

treatment. Health care workers involved in examination (ie, funduscopic examination) or procedures (eg, intubation, bronchoscopy, and suctioning of endotracheal secretions) on patients with suspected bacterial meningitis should wear surgical masks to prevent potential exposure to droplet particles. Individuals entering the room should wear standard masks if working within 3 ft of the patient. If transport is required, the patient should wear a mask to minimize the potential spread of infection. Because the etiology of bacterial meningitis is typically unknown at the time of presentation, all patients with suspected meningitis should initially be placed on droplet precautions in addition to standard precautions.

Nosocomial Central Nervous System Infections

Health care–associated ventriculitis and meningitis include infectious processes that occur in individuals who have undergone neurosurgery or the insertion of a CNS device, such as CSF drains, shunts, intrathecal pumps, and deep brain stimulators.

Health care–associated meningitis after neurosurgical procedures is typically caused by gram-negative organisms, coagulase-negative staphylococcal species (CoNS), and *Staphylococcus aureus*. *Candida* spp. have been implicated in up to 5% of cases. CSF shunt infections are usually caused by CoNS or other skin flora, with over 60% of the infections occurring within the first month. Hematogenous spread or retrograde infection from the distal end (for ventriculoperitoneal shunts) are other possible infection routes. Temporary catheters, such as external ventricular drains, can similarly become infected with either skin flora or resistant microorganisms acquired from the hospital environment. Clinical presentation can be subtle with an indolent course, especially when CoNS or *Cutibacterium acnes* are involved. The most frequent symptoms are new headaches, nausea, lethargy, seizures, fever, or a change in mental status. Detecting a change in mental status can be challenging, depending on the baseline level of consciousness. Some individuals may present with hydrocephalus due to shunt

malfunction from bacterial biofilm production or abdominal tenderness/peritonitis in ventriculoperitoneal shunts. Fever is often present, albeit less commonly in immunosuppressed individuals. Patients might also have erythema and tenderness over the subcutaneous shunt tubing.

CSF cell count and culture are the most important diagnostics, but there are several limitations. Up to 20% of patients may have normal CSF white blood cell counts, and an elevated cell count can also result from inflammatory or chemical meningitis. For slow-growing microorganisms, such as *C. acnes*, cultures might require prolonged incubation (7-10 days). In patients with ventriculoatrial shunts, blood cultures yield positive results in up to 90% of patients. While a positive CSF culture can confirm a diagnosis of ventriculitis, there are instances where it may reflect contamination or colonization. For patients with clinical suspicion of nosocomial CNS infections and negative CSF cultures, broad-range 16S rRNA PCR may be considered (49% positivity rate).

Empiric treatment for health care–associated CNS infections should include intravenous vancomycin and an antipseudomonal beta-lactam such as cefepime, ceftazidime, or meropenem. Antimicrobial therapy should be modified once a microorganism is isolated, and in vitro susceptibility results become available. Current IDSA guidelines recommend 10 to 14 days of antimicrobial treatment from the last positive culture, possibly longer (up to 21 days) in infections due to gram-negative bacilli (Table 37.6). Removal of an infected CSF shunt or drain should be pursued whenever feasible, and repeat CSF cultures should be negative before placing a new shunt.

TABLE 37.6 Suggested Length of Treatment for Health Care–Associated Ventriculitis or Meningitis

Etiology	Length of Treatment (d)

Etiology	Length of Treatment (d)
Coagulase-negative staphylococci *Cutibacterium acnes* *Staphylococcus aureus*	10-14 from shunt or drain removal
Gram-negative bacilli	10-21 from shunt or drain removal
If repeat cultures are positive	10-14 from first negative culture

Derived from the Infectious Diseases Society of America (IDSA) and consensus guidelines.

Intraventricular antimicrobial therapy may be considered for patients who responded poorly to systemic antimicrobial therapy alone or when the patient is unable to undergo the removal of the infected shunt or drain, although high-quality studies are lacking. Infectious Disease consultation is strongly recommended in this setting.

SUGGESTED READINGS

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38 Community-Acquired Pneumonia

Lauren Sattler and Daniel Reynolds

Community-acquired pneumonia (CAP) has an annual incidence ranging from about 1.5 to 14 cases per 1,000 person-years. Although the mortality rate is relatively low (<1%) for nonhospitalized patients, the 30-day mortality among hospitalized patients can rise to 23%, with the majority of deaths occurring in patients admitted to the intensive care unit (ICU). It is essential to determine whether the patient truly has CAP as opposed to hospital-acquired pneumonia (HAP; previously known as health care–associated pneumonia, or HCAP). HAP is defined as pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission, whereas CAP is either present on admission or presents within the first 48 hours of hospital stay. For further discussion on HAP and ventilator-associated pneumonia, please refer to Chapter 39, Nosocomial Pneumonia.

An essential step in managing patients with CAP is the initial assessment of severity, which can guide diagnostic and treatment decisions. The physician's assessment should be supplemented by severity-of-illness scores to identify patients with CAP who may need hospitalization. The Pneumonia Severity Index (PSI) is the strongly recommended scoring system according to professional guidelines (Table 38.1). Hospitalization is recommended for patients with PSI scores greater than or equal to 3 or CURB-65 scores greater than or equal to 2. Direct admission to the ICU is recommended for patients with severe CAP. The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) CAP guidelines define severe CAP as patients presenting with one of the major criteria or at least three minor criteria (see Table 38.1). The decision to admit a patient to the ICU can have significant implications, since studies have shown that patients admitted to a hospital ward but later

requiring admission to the ICU have higher morbidity and mortality than patients directly admitted to the ICU.

TABLE 38.1 Criteria for Severe Community-Acquired Pneumonia[a]

Major criteria
Respiratory failure requiring invasive mechanical ventilation
Septic shock with the need for vasopressors
Minor criteria
Respiratory rate ≥30 breaths/min[b]
Pa_{O_2}/F_{IO_2} ratio ≤250[b]
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level ≥20 mg/dL)
Leukopenia from infection (WBC count <4,000 cells/mm^3)
Thrombocytopenia (platelet count <100,000 cells/mm^3)
Hypothermia (core temperature <36 °C)
Hypotension requiring aggressive fluid resuscitation

BUN, blood urea nitrogen; ICU, intensive care unit, WBC, while blood cell.

[a]Patients who meet one major criterion or at least three minor criteria are recommended to be admitted to the ICU.

[b]Noninvasive ventilation can be substituted for respiratory rate ≥30 breaths/min or Pa_{O_2}/F_{IO_2} ratio ≤250.

Adapted from Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67.

Streptococcus pneumoniae remains the most commonly identified cause of CAP, although its frequency is declining, partly due to the widespread use of pneumococcal vaccines and decreased rates of cigarette smoking. Other pathogens implicated in CAP include *Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, Pseudomonas aeruginosa*, other gram-negative bacilli, and atypical bacteria (*Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*). Of note, emerging

evidence demonstrates an increased incidence of both *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA) in the community. According to the ATS/IDSA guidelines, risk assessment should be performed for individual patients upon admission, and Gram stain with culture should be obtained to assess for these pathogens in patients presenting with severe CAP. Viruses such as influenza, respiratory syncytial virus, parainfluenza, human metapneumovirus, adenovirus, coronavirus, and rhinovirus have also been implicated in CAP.

While not recommended for all patients with CAP, routine testing to determine the etiology of CAP is recommended for hospitalized patients or those suspected to have pathogens that could alter decisions regarding empirical treatment, particularly in patients receiving empiric treatment for *P. aeruginosa* or MRSA. These tests should include, at a minimum, Gram staining and culture of sputum or endotracheal aspirate for intubated patients, blood cultures, and *Legionella* and pneumococcal urinary antigens. Multiplex polymerase chain reaction (PCR) assays for both bacterial and viral respiratory pathogens have become increasingly available for routine use on both sputum and bronchoalveolar lavage (BAL) samples. For patients undergoing bronchoscopy, bronchial washings and BAL samples can be sent and tested for Gram stain, cultures, and multiplex PCR assays as mentioned earlier. It is important to note that antibiotic therapy should not be delayed in favor of collecting samples for laboratory testing. Sputum culture results are particularly helpful when an organism not part of the normal flora is recovered. Blood cultures should preferably be obtained prior to the administration of antibiotics. Obtaining blood cultures within 24 hours of admission has been shown to reduce mortality simply because resistant pathogens are identified earlier with the availability of culture results. Routine testing with a *Legionella* urine antigen test is not recommended, except in patients with severe CAP. Of note, this diagnostic test only detects *L. pneumophila* serogroup 1, so a negative result does not rule out *Legionella* pneumonia. A pneumococcal urinary antigen assay may also help in diagnosing pneumococcal pneumonia, but it is not as reliable as the *Legionella*

urine antigen assay, with a sensitivity of only 50% to 80%. During influenza season, rapid antigen or PCR assay testing for the presence of influenza A or B virus is recommended for both treatment and epidemiologic purposes. Additionally, testing for SARS-CoV-2, the virus responsible for COVID-19, is recommended for all patients presenting with pneumonia.

For patients deemed adequate for outpatient treatment (ie, those with nonsevere pneumonia, PSI score of I or II, and those who can reliably take oral medications) and who have no comorbidities or prior isolation of *Pseudomonas* or MRSA, macrolides or doxycycline are recommended. In patients with other comorbidities, such as diabetes mellitus, chronic renal and liver disease, heart failure, and other immunocompromising conditions, a respiratory fluoroquinolone (eg, moxifloxacin, levofloxacin) or a beta-lactam plus macrolide or doxycycline is preferred. For patients hospitalized in a non-ICU setting, a respiratory fluoroquinolone or beta-lactam plus macrolide can be given. Patients admitted to the ICU should receive at least the combination of a beta-lactam plus macrolide, which should cover the overwhelming majority of pathogens associated with CAP. However, empiric treatment for *Pseudomonas* or MRSA should be initiated in patients with prior respiratory isolation of these pathogens, recent hospitalization, or locally validated risk factors for *Pseudomonas* or MRSA (Table 38.2). In patients with complicated influenza infection, oseltamivir or zanamivir is recommended, ideally within 48 hours of symptoms onset. Of note, in patients with radiographic evidence of CAP who test positive for influenza, initial standard antibacterial treatment should be initiated with rapid de-escalation depending on the clinical course. Daptomycin does not achieve therapeutic concentrations in the lung and should not be considered for *S. aureus* pneumonia treatment. In patients admitted to the hospital, the first dose of antibiotics should be administered at the first point of contact; for those in the emergency department, the first dose should be given there. The recommended duration of treatment is no less than 5 days in patients receiving treatment in the outpatient setting or in hospitalized patients with a prompt response. However, CAP from *S. aureus* or gram-negative bacilli tends to

cause more severe disease than usual pathogens, so clinicians generally choose a more prolonged course. *Staphylococcus aureus* pneumonia is generally treated for 2 to 4 weeks, while *S. aureus* CAP with bacteremia, without evidence of endocarditis, is usually treated for 4 weeks. Patients should be assessed daily, and treatment should be switched from intravenous to oral when they are clinically improving, hemodynamically stable, and able to ingest medications.

TABLE 38.2 Antibiotic Recommendations for the Treatment of Severe Bacterial Community–Acquired Pneumonia

Standard regimen (no prior isolation of MRSA or *Pseudomonas*)	**Recommended antibiotics** Beta-lactam[a] plus azithromycin OR Beta-lactam[a] plus respiratory fluoroquinolone[b] OR Respiratory fluoroquinolone[b] plus aztreonam (if penicillin allergic)
Prior respiratory isolation of *Pseudomonas*, recent hospitalization or locally validated risk factors for *Pseudomonas*	**Recommended antibiotics** Piperacillin-tazobactam (4.5 g every 6 h) OR Cefepime (2 g every 8 h) OR Ceftazidime (2 g every 8 h) OR Imipenem (500 mg every 6 h) OR

	Meropenem (1 g every 8 h) OR Aztreonam (2 g every 8 h)
Prior respiratory isolation of MRSA, recent hospitalization or locally validated risk factors for MRSA	Vancomycin (15 mg/kg every 12 h, adjust based on levels) OR Linezolid (600 mg every 12 h) OR Ceftaroline (600 mg IV every 12 h) *Daptomycin cannot be used

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus* aureus.

[a]Cefotaxime, ceftriaxone, ampicillin-sulbactam.

[b]Levofloxacin (750 mg) or moxifloxacin.

*Daptomycin cannot be used because it does not have activity against pulmonary infections

Adapted from Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67; Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27-S72.

If there is clinical deterioration after 24 hours of therapy, several possibilities should be considered. Infection with a pathogen not covered by the empiric antibiotic regimen or with a resistant pathogen is a major cause of apparent antibiotic failure, which could be addressed by reassessing microbiologic results. Antibiotic therapy should be tailored based on culture and sensitivity results. Further testing for other pathogens can be performed as indicated by specific risk factors or exposures. The patient's history should be reviewed again for certain exposures, such as contact with cattle, sheep, or goat for *Coxiella burnetii*, birds for *Chlamydophila psittaci*, and rabbits for tularemia. There should also be a low threshold for

screening for human immunodeficiency virus (HIV) infection, especially in those with epidemiologic risk factors. HIV predisposes individuals to a whole gamut of opportunistic pathogens that can cause pneumonia, including *Pneumocystis jirovecii, Nocardia*, tuberculosis, cryptococcus, and endemic mycosis.

Complications of CAP should be suspected in patients who fail to respond to initial therapy. About 10% of patients with pneumococcal pneumonia develop metastatic diseases such as meningitis, arthritis, endocarditis, and peritonitis. Evaluation for a parapneumonic effusion or empyema should be considered, as drainage with a chest tube may be necessary. A repeat chest x-ray or a computed tomography scan may be warranted in patients who fail to respond to therapy. Finally, noninfectious causes such as pulmonary embolus and/or infarction, lung malignancy, hypersensitivity pneumonitis, granulomatosis with polyangiitis (Wegener granulomatosis), acute respiratory distress syndrome (ARDS), pulmonary edema, or eosinophilic pneumonia can be misdiagnosed as CAP.

SUGGESTED READINGS

Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis.* 2016;62(7):817-823.

Comprehensive molecular testing improves pathogen detection in those with CAP, potentially leading to early deescalation from empiric therapy to pathogen-directed therapy.

Isturiz R, Webber C. Prevention of adult pneumococcal pneumonia with the 13-valent pneumococcal conjugate vaccine: CAPiTA, the community-acquired pneumonia immunization trial in adults. *Hum Vaccin Immunother*. 2015;11(7):1825-1827.

Large, randomized, and placebo-controlled trial demonstrating efficacy of the pneumococcal conjugate vaccine (PCV13) in adults 65 years and older.

Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med.* 2015;373:415-427.

Population-based surveillance study showing the incidence of CAP requiring hospitalization in the adult population.

39 Nosocomial Pneumonia

Richard F. Van Besien and Marin H. Kollef

Nosocomial pneumonia (NP) is comprised of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). It is the second most common hospital-acquired infection (after urinary tract), though it carries the highest mortality. VAP affects approximately 1 in 10 patients on the ventilator and is associated with increased mortality, prolonged hospital stays, and excess costs of tens of thousands of dollars per case.

HAP is defined as an NP that develops 48 hours or more after hospital admission, which was not incubating at the time of admission and is not associated with mechanical ventilation (Table 39.1). VAP refers to NP that manifests more than 48 hours after endotracheal intubation. The 48-hour distinction is derived from potential differences in causative organisms, with usual community-acquired organisms predominating before the 48-hour mark and hospital-acquired resistant pathogens such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) more common thereafter (Table 39.2). The category of health care–associated pneumonia was eliminated in the 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines; however, it is important to recognize that patients with multiple recent hospitalizations or antibiotic exposures and prior colonization or infection with multidrug-resistant pathogens are at an increased risk of carrying antibiotic-resistant organisms. One must consider individualized risk factors when choosing initial antibiotics.

TABLE 39.1 Definitions of Pneumonia (With Focus on Bacterial Pathogens)

Pneumonia Category	Definition
Community-acquired pneumonia (CAP)	Patients with a first positive bacterial culture obtained within 48 h of hospital admission lacking risk factors for health care–associated pneumonia
Hospital-acquired pneumonia (HAP)	Patients with a first positive bacterial culture >48 h after hospital admission
Ventilator-associated pneumonia (VAP)	Mechanically ventilated patients with a first positive bacterial culture >48 h after hospital admission or tracheal intubation, whichever occurred first
Ventilated hospital-acquired pneumonia (vHAP)	Subset of HAP that is severe enough to warrant endotracheal intubation. Associated with worse outcomes compared to nonventilated HAP

Criteria for pneumonia include new or progressive lung infiltrate and at least two of the following clinical criteria: hyperthermia or hypothermia, elevated white blood cell count, purulent tracheal secretions or sputum, and worsening oxygenation.

TABLE 39.2 Most Common Pathogens Associated With Various Pneumonia Categories

Infection Site	Pathogens
I. Pneumonia (immunocompetent)	
1. Community-acquired pneumonia (nonimmunocompromised host)	*Streptococcus pneumonia, Haemophilus influenzae* *Moraxella catarrhalis, Mycoplasma pneumoniae* *Legionella pneumophila, Chlamydia pneumoniae* Methicillin-resistant *Staphylococcus aureus* (MRSA) Influenza virus/other respiratory viruses[a]

Infection Site	Pathogens
2. HAP or VAP	Methicillin-resistant *S. aureus* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Acinetobacter* species *Stenotrophomonas* species *L. pneumophila*
3. Pneumonia (immunocompromised host)	
a. Neutropenia	Any pathogen listed previously *Aspergillus* species *Candida* species (rare)
b. Human immunodeficiency virus (uncontrolled)	Any pathogen listed previously *Pneumocystis carinii* *Mycobacterium tuberculosis* *Histoplasma capsulatum* Other fungi
c. Solid-organ transplant or bone marrow transplant	Any pathogen listed previously (Can vary depending on the timing of infection to transplant)
d. Cystic fibrosis	*H. influenzae* (early) *S. aureus* *P. aeruginosa* *Burkholderia cepacia*
4. Lung abscess	*Bacteroides* species *Peptostreptococci* *Fusobacterium* species *Nocardia* (in immunocompromised patients) Amebic (when suggestive by exposure)

Infection Site	Pathogens	
5. Empyema	*S. aureus* *S. pneumoniae* Group A Streptococci *H. influenzae*	Usually acute
	Anaerobic bacteria *Enterobacteriaceae* *M. tuberculosis*	Usually subacute or chronic

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.
[a]Respiratory syncytial virus (RSV), COVID-19, parainfluenza virus, adenovirus, human metapneumovirus, non-COVID coronavirus, rhinovirus/enterovirus.

NP is caused by oropharyngeal aspiration. Critical illness is known to induce changes in the oropharyngeal epithelium, altering the flora to harbor more gram-negative species and other resistant organisms that may be acquired from the hospital environment. The endotracheal tube, along with a decrease in airway protective reflexes (due to sedation or altered mental status), facilitates aspiration to the lower respiratory tract. NP should be suspected if there is a new radiographic infiltrate coupled with at least two of the following clinical signs: fever/hypothermia, leukocytosis, increased sputum production, or increased oxygen requirement. Table 39.3 lists other conditions that should be considered in the differential diagnosis.

TABLE 39.3 Noninfectious Causes of Fever and Pulmonary Infiltrates Mimicking Nosocomial Pneumonia

Chemical aspiration without infection
Atelectasis
Pulmonary embolism
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung contusion

Infiltrative tumor
Radiation pneumonitis
Drug reaction
Cryptogenic organizing pneumonia

Immediate collection of blood and respiratory cultures and administration of empiric antibiotics are essential (Table 39.4 and Algorithm 39.1), as adequate initial therapy improves outcomes in NP and other serious infections. A tracheal aspirate is usually sufficient for culturing the respiratory tract, and the 2016 IDSA/ATS guidelines note that bronchoscopic sampling has not been shown to improve outcomes. However, it is prudent to perform bronchoscopy with bronchoalveolar lavage in immunosuppressed patients, if there is suspicion of unusual organisms, or if less invasive testing is nondiagnostic.

TABLE 39.4 Antibiotic Recommendations for Nosocomial Pneumonia

Category of Pneumonia	Organisms	Empiric Therapy	Additional Information

Category of Pneumonia	Organisms	Empiric Therapy	Additional Information
HAP/VAP Not at risk for MDR pathogens and hospitalized <5 d	Non-MDR-resistant potential pathogens: *Streptococcus pneumonia* *Haemophilus influenzae* *Methicillin-sensitive Staphylococcus aureus* *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* species *Proteus* species *Serratia marcescens*	Third-generation cephalosporin (ceftriaxone) Or Ampicillin-sulbactam Or Respiratory fluoroquinolone (levofloxacin or moxifloxacin) Or Nonantipseudomonal carbapenem (ertapenem)	Azithromycin should be considered for atypical coverage in very ill patients or ones with a high suspicion for atypical organisms or *Legionella* who are not on a respiratory fluoroquinolone.
HAP/VAP At risk for MDR pathogens or hospitalized for ≥5 d	Potential MDR pathogens: *Pseudomonas aeruginosa*	Antipseudomonal cephalosporin (cefepime, ceftazidime, cefiderocol[a]) Or	Carbapenems are often effective against ESBL organisms (*E. coli, Klebsiella*) or *Acinetobacter*. Ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, and imipenem-cilastatin-relebactam can be used for MDR infections but should be reserved only for culture-proven

Category of Pneumonia	Organisms	Empiric Therapy	Additional Information
			infections or patients at high risk for such infections.
	K. pneumonia (extended-spectrum beta-lactamase +)	Antipseudomonal carbapenem (imipenem or meropenem). If resistant organism, imipenem-cilastatin-relebactam. Or	
	Acinetobacter species *Legionella pneumophila* MRSA Metallo-beta-lactamase producers (such as NDM-1)[b]	Antipseudomonal penicillin with beta-lactamase inhibitor (piperacillin-tazobactam, ceftazidime-avibactam, or ceftolozane-tazobactam) Plus Aminoglycoside (gentamycin, tobramycin, or amikacin)[c] Plus Anti-MRSA agent (linezolid, vancomycin, or ceftaroline)	For patients with penicillin allergy consider substituting beta-lactam with: • Aztreonam • Meropenem (<1% cross-reactivity to penicillin allergy) Inhaled antibiotics (colistin and aminoglycosides) have been used in select populations and should be used only after consultation with a subspecialist.

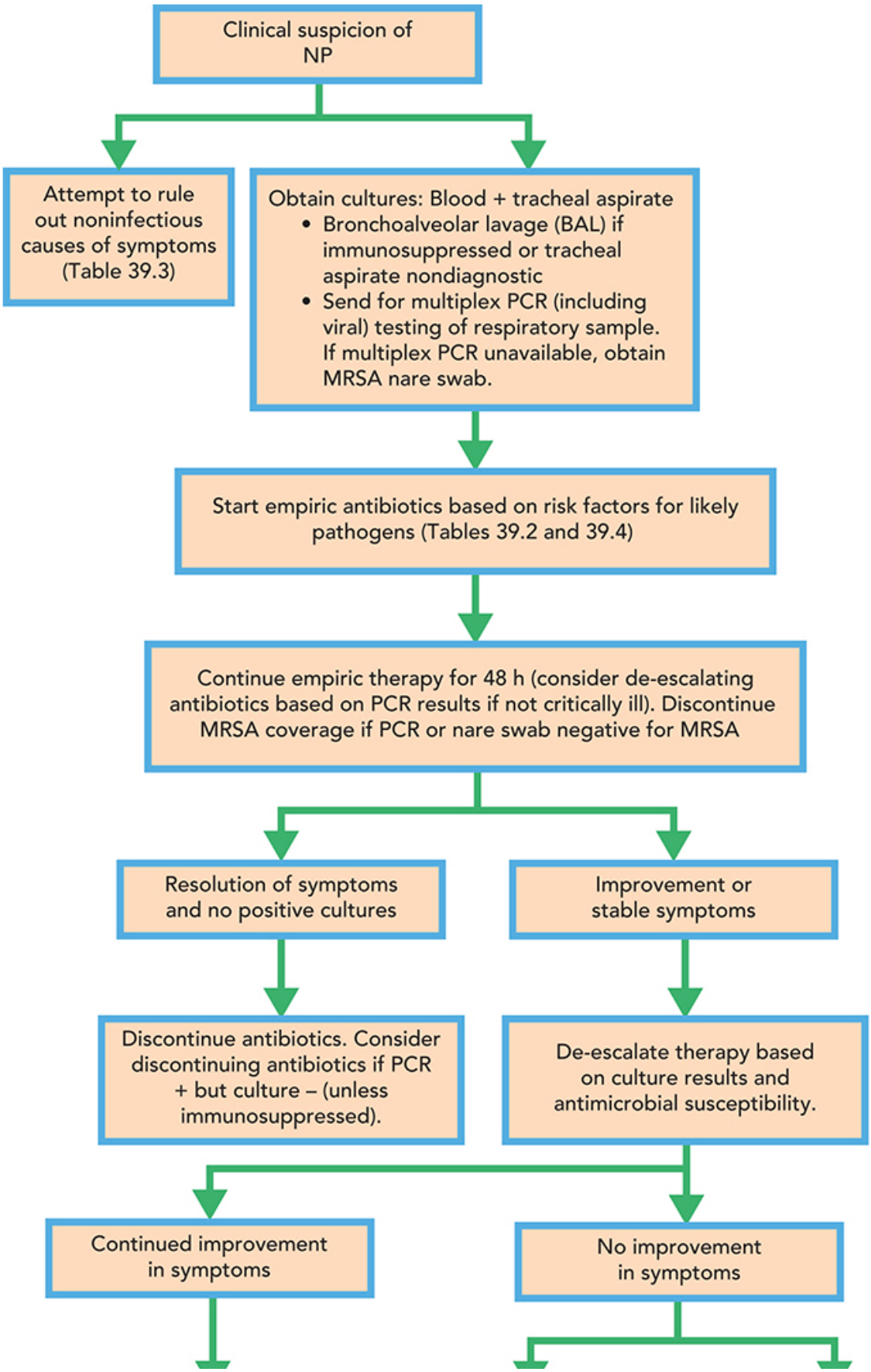
Clinicians should be aware of the prevailing bacterial pathogens associated with NP and the antibiotic susceptibility patterns of these pathogens according to the local antibiogram whenever possible.

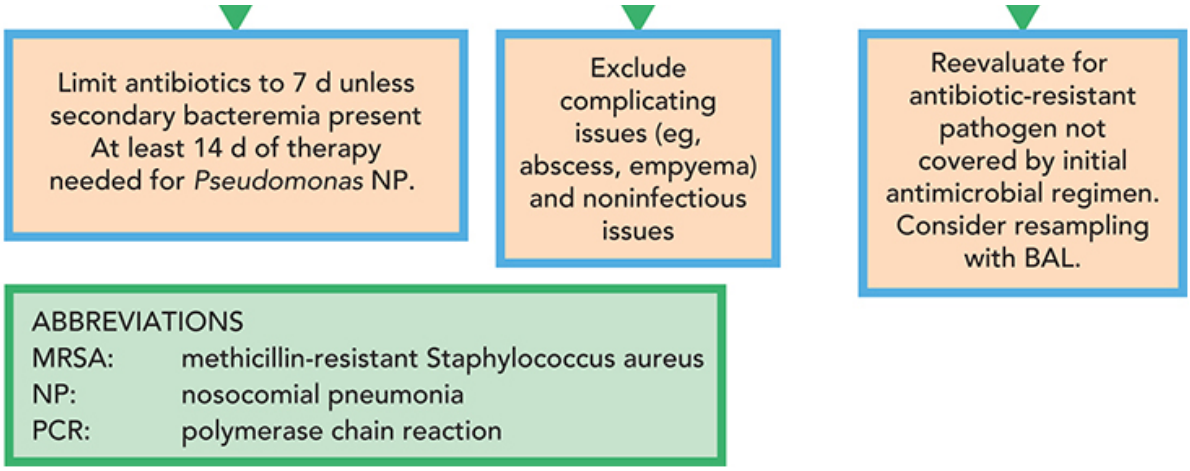
ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus;* NDM-1, New Delhi metallo-beta-lactamase-1; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

[a]Cefiderocol can be used for resistant gram-negative NP.

[b]Ceftazidime-avibactam plus aztreonam with expert consultation recommended.
[c]Aminoglycoside is recommended as the choice of additional coverage for patients at risk of MDR pathogens over fluoroquinolones as most institutions have high resistance rates for fluoroquinolones.

ALGORITHM 39.1 A Step-by-Step Approach to the Management of Nosocomial Pneumonia


Clinical suspicion of NP
Attempt to rule out noninfectious causes of symptoms (Table 39.3)
Obtain cultures: Blood + tracheal aspirate
• Bronchoalveolar lavage (BAL) if immunosuppressed or tracheal aspirate nondiagnostic
• Send for multiplex PCR (including viral) testing of respiratory sample. If multiplex PCR unavailable, obtain MRSA nare swab.
Start empiric antibiotics based on risk factors for likely pathogens (Tables 39.2 and 39.4)
Continue empiric therapy for 48 h (consider de-escalating antibiotics based on PCR results if not critically ill). Discontinue MRSA coverage if PCR or nare swab negative for MRSA
Resolution of symptoms and no positive cultures
Improvement or stable symptoms
Discontinue antibiotics. Consider discontinuing antibiotics if PCR + but culture – (unless immunosuppressed).
De-escalate therapy based on culture results and antimicrobial susceptibility.
Continued improvement in symptoms
No improvement in symptoms


Limit antibiotics to 7 d unless secondary bacteremia present At least 14 d of therapy needed for *Pseudomonas* NP.
Exclude complicating issues (eg, abscess, empyema) and noninfectious issues
Reevaluate for antibiotic-resistant pathogen not covered by initial antimicrobial regimen. Consider resampling with BAL.
ABBREVIATIONS
MRSA: methicillin-resistant Staphylococcus aureus
NP: nosocomial pneumonia
PCR: polymerase chain reaction

MRSA: methicillin-resistant *Staphylococcus aureus;* NP: nosocomial pneumonia; PCR: polymerase chain reaction.

In recent years, multiplex polymerase chain reaction (PCR) testing has emerged as a diagnostic tool in NP. As opposed to traditional bacterial culturing which can take days to result, PCR testing provides reliable identification of pathogen DNA in a few hours. It is best used to hasten antibiotic de-escalation, such as stopping anti-MRSA coverage if the PCR probe for genes conferring methicillin resistance is negative. PCR results should be correlated with the culture as sometimes low levels of bacterial DNA are detected that are not clinically meaningful, and in such cases, antibiotics can usually be ceased. MRSA nare PCR can also facilitate antibiotic stewardship as the negative predictive value is 94.8% in VAP. Antibiotic de-escalation is important to prevent selective pressure for antibiotic resistance in the hospital setting. Seven days is the usual duration of therapy for immunocompetent individuals, based on a landmark study indicating that shorter courses are as effective as longer courses. Bacteremic patients typically require a longer duration of therapy, and at least 14 days of antibiotics are needed for pseudomonal NP to prevent relapse.

It should be noted that a significant portion of NP is caused by viruses, particularly in the era of COVID-19. Fungal infection is unusual in immunocompetent individuals, though *Aspergillus* complicating COVID-19 pneumonia has been well described and

fungal pathogens should be considered in those treated with immunosuppressive agents or if there is failure to improve with usual antibacterial therapy.

Much attention has been paid to the prevention of VAP, though high-quality evidence of effective interventions is mostly lacking. The most important prevention strategy is daily reevaluation of the need for ongoing mechanical ventilation with performance of spontaneous breathing trials and subsequent extubation if successful. There is some evidence for selective oropharyngeal and gut decontamination with nonabsorbable antibiotics in order to decrease the oropharyngeal and intestinal bacterial burden, although this appears to be most effective in hospitals with low rates of infection with multidrug-resistant bacteria. Head of bed elevation, secretion clearance, and adherence to infection prevention practices (hand hygiene and gown/glove wearing) may also be beneficial. Traditionally, it has been thought that gastric acid suppression increases the risk of NP by diminishing the sterilizing effect of the stomach and thus causing aspiration of a larger pathogen inoculum. However, analysis of the SUP-ICU trial reveals that those randomized to pantoprazole had a similar incidence of infectious complications as those randomized to placebo. Nonetheless, cessation of H2 blocker or proton pump inhibitor when no longer indicated should be a routine part of intensive care.

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40 Cellulitis/Fasciitis/Myositis

Jason P. Burnham

Severity of illness due to skin and soft tissue infections (SSTIs) loosely correlates with the depth of skin structure involvement. Terminology based on anatomic depth continues to be widely used (Figure 40.1). Patients with superficial infections involving only the epidermis and dermis, such as impetigo, ecthyma, erysipelas, folliculitis, furuncles, and carbuncles, rarely need admission to the intensive care unit. In contrast, deeper soft tissue infections, including cellulitis, fasciitis, and myositis, are associated with significant morbidity and mortality, particularly in immunocompromised hosts.

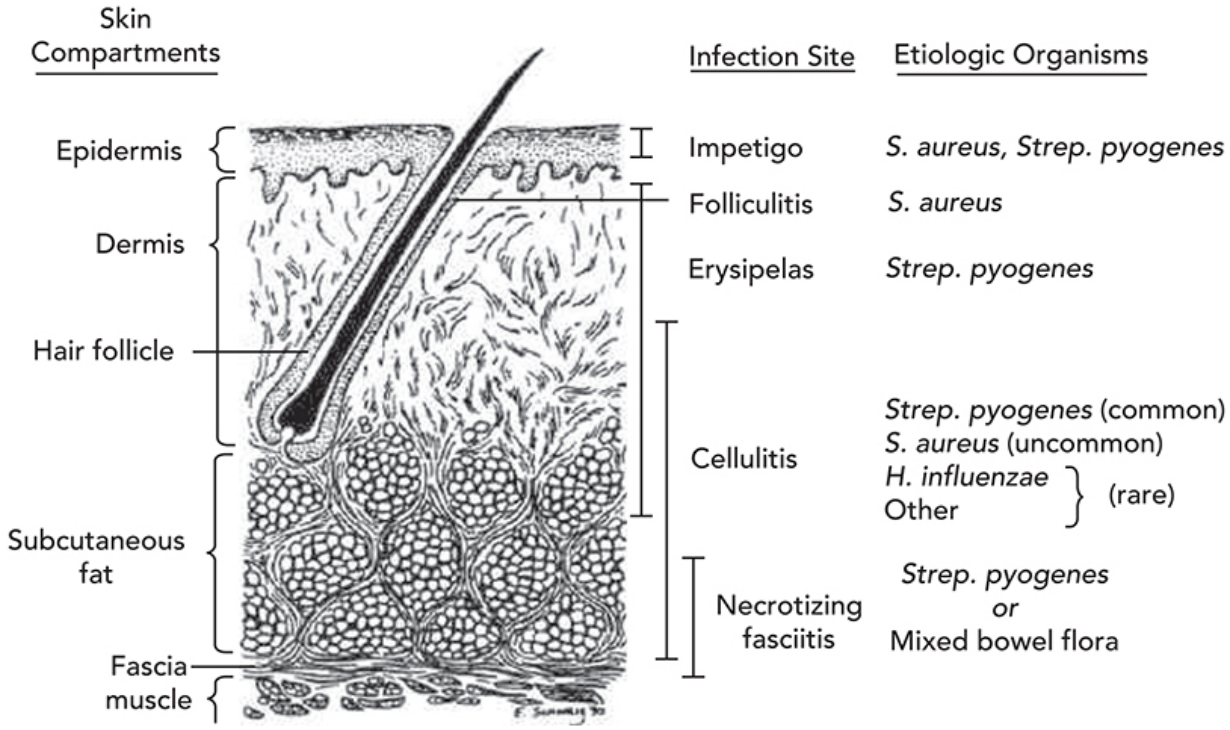


FIGURE 40.1 Anatomic classification of soft tissue infections.

Cellulitis

Cellulitis is an acute bacterial infection involving the skin and subcutaneous tissue that is characterized by diffuse-spreading erythema and can be associated with lymphangitis. The disease most commonly involves the lower extremities, but other areas that may be affected include the periorbital regions, areas near body piercings, incisions, puncture wounds ("skin-popping"/illicit drug injection sites), bites, and areas with any preexisting skin conditions such as venous stasis, ischemia, or decubitus ulcers. Patients who are critically ill may have increased susceptibility to these infections because of their impaired immune status and altered skin flora. The most common causative organisms are beta-hemolytic streptococci (BHS) and *Staphylococcus aureus.* In patients with cellulitis and no culture evidence of BHS infection, the vast majority respond to therapy directed against BHS. Less common causes of cellulitis may be suspected based on the patient's medical history or comorbidities (Table 40.1).

TABLE 40.1 Less Common Sources of Soft Tissue Infections

History	Source
Fresh or brackish water with laceration or abrasion	*Aeromonas hydrophila*
Salt water or seafood contamination of wound, seafood consumption	*Vibrio* species (especially *Vibrio vulnificus*)
Cat/dog bite	*Pasteurella multocida, Capnocytophaga canimorsus* (dogs), polymicrobial anaerobes
Human bite	Streptococci, *Eikenella* spp., polymicrobial anaerobes

Necrotizing Fasciitis

Necrotizing fasciitis is a rare SSTI that involves the deep fascia and always requires surgical intervention and broad-spectrum intravenous antimicrobials. Rates of necrotizing fasciitis vary widely based on region (0.18-15.5 per 100,000) and seem to be increasing over time. Type I necrotizing fasciitis is polymicrobial, including both aerobic and anaerobic organisms. Type II necrotizing fasciitis is classically caused by *Streptococcus pyogenes*, although *S. aureus* also falls into this category. There are a variety of case reports and case series of less frequently encountered agents causing necrotizing fasciitis, making it important for practitioners to realize the importance of surgical debridement with attendant bacterial cultures in combination with broad-spectrum antimicrobials as the first lines of therapy.

Though the classic teaching for necrotizing fasciitis is pain out proportion to physical examination findings, it is important to remember that superficial nerves can undergo necrosis, resulting in anesthesia of affected areas (see Table 40.2). Eliciting a history may be problematic due to the severity of illness and alterations in sensorium, requiring maintenance of a high degree of suspicion for necrotizing SSTIs. Imaging findings cannot rule out necrotizing fasciitis (due to unacceptably low sensitivity) and may delay surgical intervention, which is associated with poor outcomes. Necrotizing fasciitis predominantly affects the lower extremities, with predisposing conditions (diabetes, abnormalities of venous return or arterial insufficiency, and intravenous drug use) explaining the predilection for this anatomic localization. Due to the relative rarity, heterogeneity of microbiologic causes, and severity of disease, no clinical trials are available to guide duration of therapy, although guidelines based on expert opinion suggest continuation of therapy directed against cultured organisms for at least 48 to 72 hours after patients are clinically stable and require no further operative interventions.

TABLE 40.2 Characteristics Associated With Increased Likelihood of Necrotizing Infection

Pain out of proportion to examination
Bullae
Systemic toxicity
Serum sodium <135 mmol/L; WBC >15,400 cell/mm^3
Tenderness beyond the area of erythema
Crepitus
Cutaneous anesthesia
Cellulitis refractory to antibiotic therapy

WBC, white blood count.

Myositis/Pyomyositis/Gas Gangrene

Myositis involves infection reaching down to the muscle and is generally differentiated into myonecrosis or pyomyositis. Myonecrosis is associated with gas gangrene and clostridial infections, while pyomyositis is almost universally due to *S. aureus.* The distinction is vital, as myonecrosis necessitates immediate operative debridement, whereas pyomyositis may be amenable to antibiotics and percutaneous drainage. Pyomyositis is characterized by localized pain in a single muscle group associated with fever. Magnetic resonance imaging (MRI) is the preferred imaging study of choice for diagnosing pyomyositis, although bedside ultrasound may be a useful rapid diagnostic alternative.

Gas gangrene or myonecrosis is caused by *Clostridium* species. *Clostridium perfringens* is classically associated with traumatic injuries; *C. septicum* with neutropenic patients or those with gastrointestinal malignancies or abnormalities, and *C. sordellii* with childbirth and "home" abortions. Additionally, *C. perfringens, C. novyi*, and *C. sordellii* are associated with drug users who practice "skin-popping." Although rare, *C. sordellii* infections are notable as they can be associated with a toxic shock-like syndrome, particularly in patients with recent parturition or abortion.

Ecthyma Gangrenosum

Ecthyma gangrenosum is an uncommon necrotizing, hemorrhagic cutaneous vasculitis that is classically associated with *Pseudomonas aeruginosa* septicemia. However, many other pathogens have also been implicated, including other gram-negative bacilli, *S. aureus*, *S. pyogenes*, fungi, molds, atypical mycobacteria, and viruses. The lesions typically begin as painless erythematous nodules that evolve into painful necrotic ulcers with eschar, predominantly seen between the umbilicus and knees. Necrosis results from invasion of the medial and adventitial blood vessel walls by the implicated microbes. Patients suspected of having ecthyma gangrenosum should be given broad-spectrum antimicrobial therapy, including an agent with antipseudomonal activity.

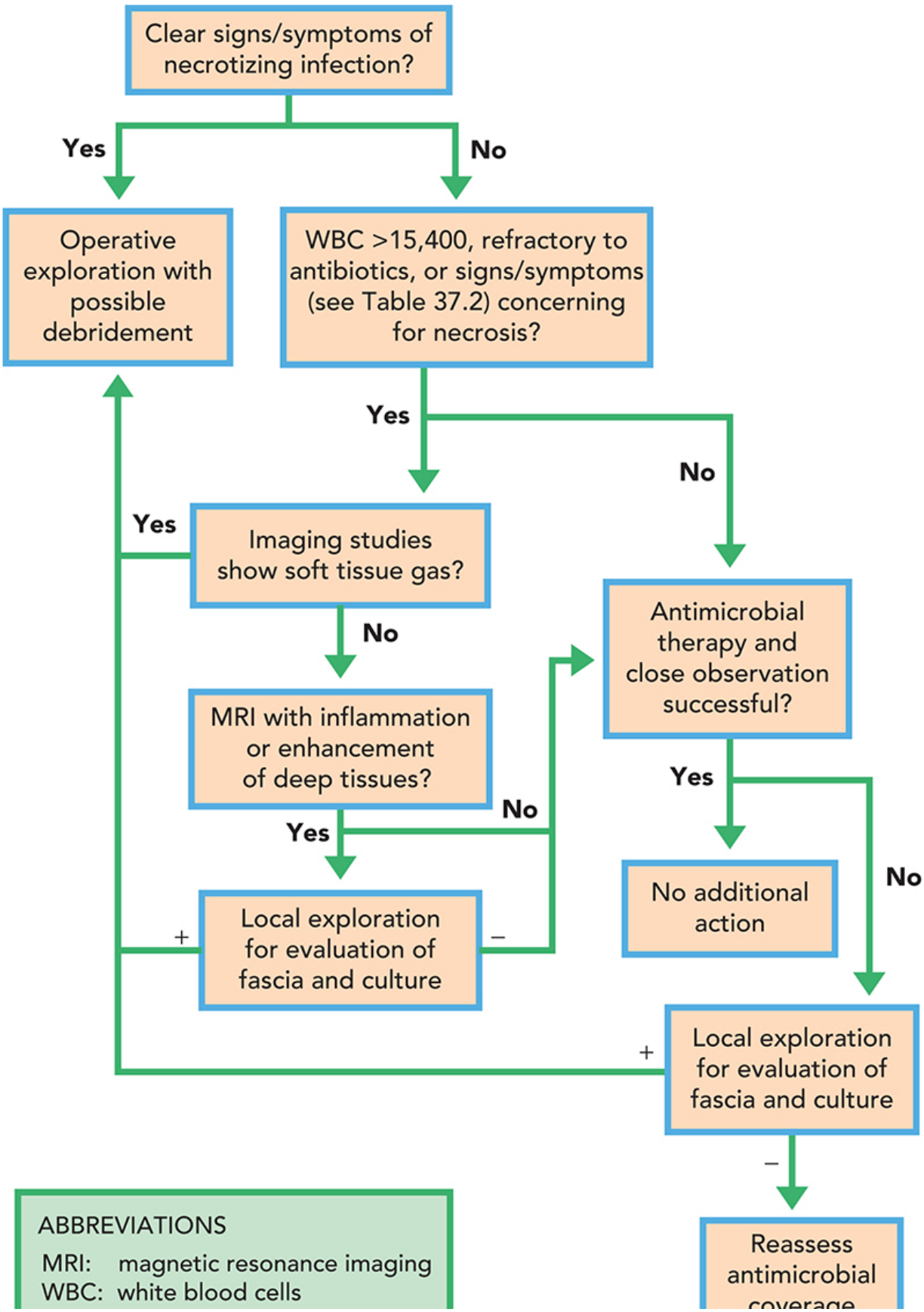
Diagnosis and Treatment of Necrotizing Infections

Determining the presence of a necrotizing infection can be challenging because physical examination is often unreliable (Table 40.2). Patients with these infections frequently have normal overlying skin, and overt signs of necrotic tissue, such as crepitus, are observed in only 30% of patients. Although laboratory abnormalities, including C-reactive protein, hemoglobin, sodium, creatinine, glucose levels, and white blood cell counts, have been used to construct risk scores, they are not widely used.

Radiographic imaging may assist in the diagnosis of necrotizing soft tissue infections. However, plain radiography shows soft tissue gas in only 15% to 30% of necrotizing infections. Computed tomography and ultrasound are sometimes helpful ancillary studies for identifying soft tissue gas or necrotic tissue. MRI may delineate the extent of the infection and has a high sensitivity for detection of necrotizing soft tissue infections; however, its specificity is somewhat low, and logistical difficulties in study availability limit its utility in

patients who are critically ill. In equivocal cases, biopsy with frozen section has been recommended for definitive diagnosis, although this is associated with significant logistical difficulties when needed urgently. An alternative means of establishing the severity of the infection is to make a bedside incision under local anesthesia and digitally examine the tissue planes; facile separation of the subcutaneous tissue from the fascia is a pathognomonic sign of necrotizing soft tissue infection. If suspicion for a necrotizing infection is high, imaging studies should not delay surgical exploration. A potential management algorithm for distinguishing necrotizing from nonnecrotizing infections is presented in Algorithm 40.1.

ALGORITHM 40.1 **Algorithm for Managing Soft Tissue Infections**


Clear signs/symptoms of necrotizing infection?
Yes
No
Operative exploration with possible debridement
WBC >15,400, refractory to antibiotics, or signs/symptoms (see Table 37.2) concerning for necrosis?
Yes
No
Yes
Imaging studies show soft tissue gas?
No
MRI with inflammation or enhancement of deep tissues?
Yes
No
Local exploration for evaluation of fascia and culture
+
–
Antimicrobial therapy and close observation successful?
Yes
No
No additional action
Local exploration for evaluation of fascia and culture
+
–
Reassess antimicrobial coverage
ABBREVIATIONS
MRI: magnetic resonance imaging
WBC: white blood cells

Antibiotic therapy directed against streptococci and staphylococci has generally been used for initial therapy of nonnecrotizing soft tissue infections. However, one-third of isolates from patients with soft tissue infections are gram-negative organisms, so additional antibiotic therapy directed against common gram-negative organisms may be needed, particularly with infections involving the axillae or perineum. Gram-negative antimicrobials are also recommended in patients with severe infections and those who are immunocompromised. Antimicrobial management of nonnecrotizing infections is complicated by the increased prevalence of resistant organisms such as methicillin-resistant *S. aureus* (MRSA), including those positive for the Panton-Valentine leucocidin toxin. MRSA accounts for 59% of the skin/soft tissue infections in patients presenting to emergency departments at 11 facilities across the country. Therefore, it is generally appropriate to include an antimicrobial agent that has activity against this organism. Vancomycin has traditionally been used for this, but linezolid, daptomycin, and ceftaroline may be alternatives in patients who are critically ill. Negative MRSA nares swabs have a high negative predictive value for SSTIs; however, this has not been studied specifically for necrotizing SSTIs. Therefore, the utility of a negative MRSA nares result for anti-MRSA therapy discontinuation requires further study.

Necrotizing soft tissue infections are lethal disorders associated with a 20% to 70% mortality. Patients with necrotizing infections require immediate surgical debridement and broad-spectrum antibiotics directed against gram-positive cocci, gram-negative bacilli, and anaerobes. For patients with monomicrobial infections due to *S. pyogenes* or clostridia, penicillin PLUS clindamycin are the definitive treatment. Agents that can decrease toxin production, such as clindamycin or linezolid, may also be useful in selected patients with necrotizing soft tissue infections.

SSTIs have a variety of presentations and can be severe enough to warrant intensive care. Practitioners should be familiar with the

spectrum of clinical presentations for SSTIs that require urgent surgical debridement to avoid delays in surgery, which can lead to worsened outcomes. Aggressive source control and broad-spectrum antimicrobials are essential for all severe SSTIs, with empiric therapy guided by knowledge of patient risk factors and the local antibiogram.

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41 Bacteremia and Catheter-Related Bloodstream Infections

M. Joshua Hendrix and David K. Warren

Bacteremia

Bacteremia is a common cause of critical illness. Bloodstream infections (BSIs) can arise from a known source of infection, a primary infection without an obvious source, or from an intravascular or indwelling device. The three key steps to approaching BSIs in patients are:

1. Identifying the causative organism
2. Determining the source of infection
3. Quickly initiating appropriate antibiotic therapy

Staphylococcus aureus, streptococcal species, and enterococci are the most common causes of gram-positive bacteremia, while *Escherichia coli* and *Klebsiella* species are the most prevalent pathogens for gram-negative bacteremia. Gram-positive organisms are likely to be associated with central venous catheters, intravenous drug use, skin and soft tissue infections, and nosocomial or prosthetic devices. For gram-negative pathogens, infections are more likely to originate from genitourinary, gastrointestinal, or nosocomial sources. *Pseudomonas*, *Serratia*, *Stenotrophomonas*, and *Acinetobacter* are often associated with nosocomial infections.

It is crucial to differentiate true BSIs from pseudo-bacteremia. This term refers to positive blood cultures with bacteria typically considered contaminants during the collection process, usually from skin or environmental flora. These organisms are often seen in a single positive blood culture. Coagulase-negative staphylococcal

species (except *Staphylococcus lugdunensis*), *Cutibacterium acnes*, *Corynebacterium*, and *Bacillus* species (not *Bacillus anthracis*) are common contaminants but can cause true BSIs in appropriate clinical contexts. Two concordant blood cultures within 48 hours should not be considered contaminants. *Staphylococcus aureus* and *Candida* species should never be considered contaminants.

The selection of antibiotics for patients with bacteremia and septicemia should be based on the probable pathogens, as determined by local antibiograms and the presence of risk factors for multidrug-resistant organisms. Prompt initiation of effective therapy is vital, as delays can lead to poorer outcomes. While broader antibiotics, such as vancomycin, piperacillin-tazobactam, and cefepime, are often used during the acute phase of infection before a causative organism can be identified, more targeted, narrow-spectrum antibiotics can be equally or more effective. As identification and susceptibility testing become available, it is important to adjust antibiotic choices to optimize outcomes, reduce unnecessary antibiotic exposure, and minimize the risk of unwanted side effects.

Certain organisms, such as *S. aureus*, *Streptococcus intermedius* (formerly known as *Streptococcus milleri* group), and *Klebsiella pneumonia*, are more likely to be associated with secondary or multiple sites of infection, especially in cases of high-grade bacteremia. A thorough history and physical examination are essential for better identification of these sites. Metastatic complications can include endocarditis, thrombophlebitis, brain and visceral abscesses, as well as infections involving the spine, joints, and indwelling hardware or devices. Suspecting these metastatic sites of infection becomes crucial when there is a delay in initiating antibiotics or when persistent fever and repeatedly positive blood cultures occur despite appropriate antibiotic treatment.

The treatment of bacteremia requires both appropriate antibiotic therapy and the identification and control of the source of infection. Whenever possible, removing or exchanging infected central lines, draining abscesses, and irrigating and debriding wounds are

essential measures. Surgical intervention should be considered and approached when appropriate.

Central Line–Associated Bloodstream Infections

Central line–associated bloodstream infections (CLABSIs) are potential complications of central venous catheters (CVCs). CLABSIs are usually caused by bacteria colonizing both the intra- and extraluminal portions of the catheter or the catheter hub, subsequently entering the bloodstream. CVCs can also become contaminated through hematogenous seeding from other sources, including cellulitis and bacteremia from other causes.

The diagnosis of CLABSIs can be challenging, because local inflammation and/or purulent drainage at the insertion site may not always be present. Various practical strategies have been suggested to improve the accuracy of CLABSI diagnosis, but none exhibit sufficient sensitivity or specificity to be used as sole diagnostic criteria. Blot et al. found that in CLABSIs, a blood culture drawn from a catheter grew faster than a paired sample from a peripheral venipuncture. If a catheter-drawn blood culture shows positive growth at least 2 hours earlier than a peripherally drawn culture obtained at the same time, it may suggest that the catheter was the source of the bacteremia. However, these findings are dependent on the collected blood volume and the time until incubation of each individual culture.

An approach to suspected catheter-associated BSIs in the intensive care unit is presented in Algorithm 41.1. Management strategies for specific pathogens are shown in Table 41.1. Special care should be taken in cases involving *Candida* species and *S. aureus*, given their ability to establish metastatic foci of infection. High rates of endocarditis have been reported in catheter-associated *S. aureus* bacteremia. While transthoracic echocardiography has only a moderate degree of sensitivity, transesophageal echocardiography should be considered if the former does not show

evidence of endocarditis, but clinical suspicion for endocarditis remains high, as long as no contraindications exist.

ALGORITHM 41.1 Evaluation of Suspected Catheter-Associated Bacteremia

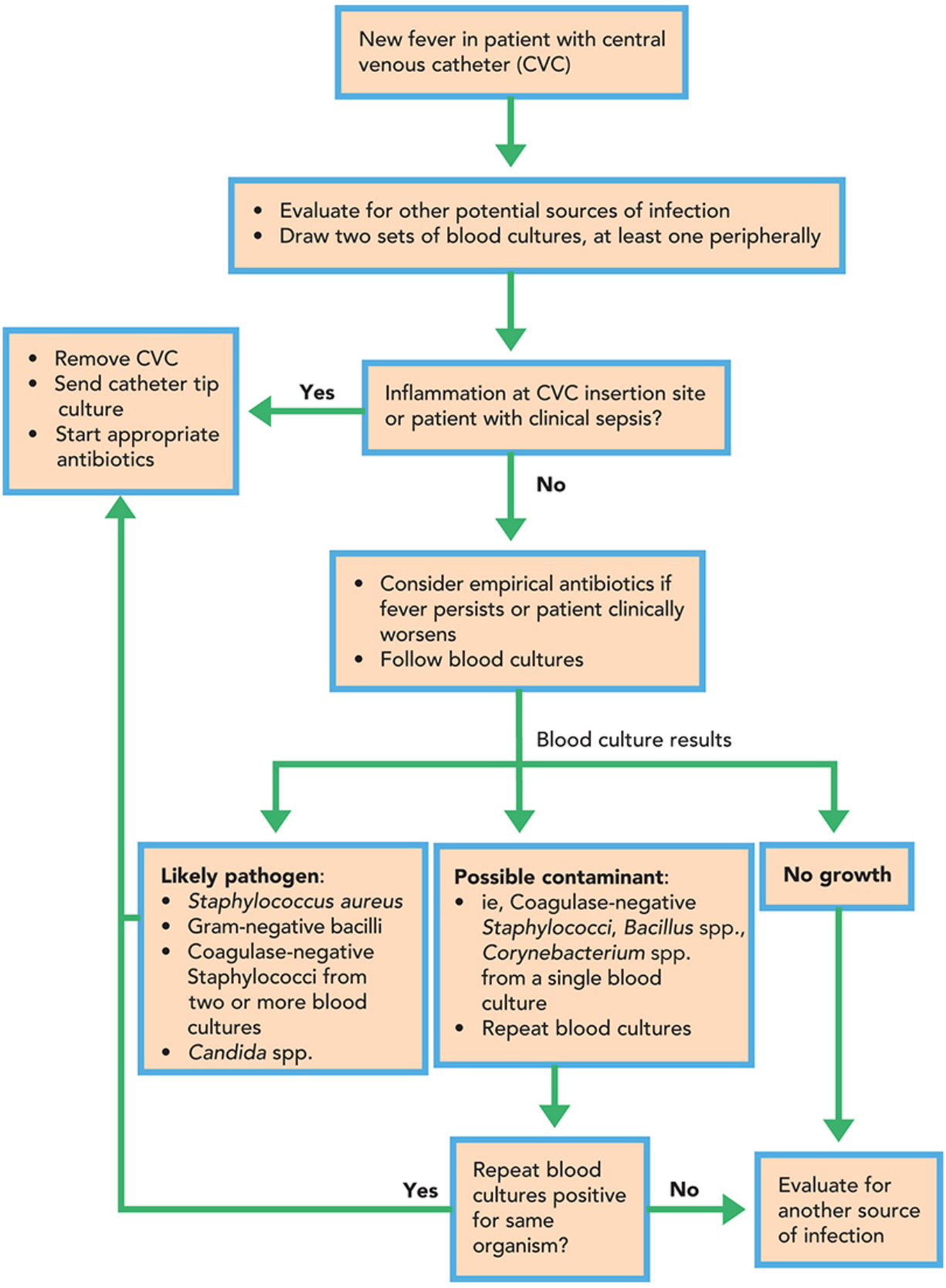
New fever in patient with central venous catheter (CVC)
Evaluate for other potential sources of infection
Draw two sets of blood cultures, at least one peripherally
Inflammation at CVC insertion site or patient with clinical sepsis?
Yes
Remove CVC
Send catheter tip culture
Start appropriate antibiotics
No
Consider empirical antibiotics if fever persists or patient clinically worsens
Follow blood cultures
Blood culture results
Likely pathogen:
Staphylococcus aureus
Gram-negative bacilli
Coagulase-negative Staphylococci from two or more blood cultures
Candida spp.
Possible contaminant:
ie, Coagulase-negative Staphylococci, Bacillus spp., Corynebacterium spp. from a single blood culture
Repeat blood cultures
No growth
Repeat blood cultures positive for same organism?
Yes
No
Evaluate for another source of infection

TABLE 41.1 Management of Bloodstream Infections by Common Pathogens

Staphylococcus aureus

Use parenteral beta-lactams (oxacillin or nafcillin) for susceptible strains.
Use vancomycin for MRSA only.
Linezolid and daptomycin are acceptable alternatives for MRSA if unable to tolerate vancomycin.
Transesophageal echocardiogram (TEE) recommended, if possible, evaluating for endocarditis.
Remove catheters.
If endocarditis ruled out by TEE, blood cultures are negative within 72 h of treatment, no prosthetic material in place and catheter removed, treat for 14 d; otherwise treat for ≥4 wk.
Treat complicated infections (endocarditis, septic thrombophlebitis, prolonged bacteremia) for 4-6 wk (6-8 wk for osteomyelitis).

Coagulase-negative Staphylococci

If catheter removed, treat with vancomycin for 5-7 d after removal.
If catheter must be retained, treat for 10-14 d with vancomycin, consider antibiotic lock, and repeat blood cultures if signs or symptoms recur.

Enterococci

Ampicillin for susceptible isolates.
Vancomycin for ampicillin-resistant, vancomycin-sensitive isolates.
Linezolid or daptomycin for vancomycin-resistant, ampicillin-resistant isolates.
Consider addition of synergy-dosed gentamicin (1 mg/kg IV q8h).
Remove catheters if possible.
Treat for 7-14 d of systemic antibiotic therapy for uncomplicated infection.

Gram-negative bacilli

Empiric therapy should include agents active against *Pseudomonas aeruginosa.*
Tailor antibiotics to sensitivity results.
Remove catheter, especially with *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* spp.
If catheter removed, treat for 10-14 d of systemic antibiotic therapy; if catheter must be retained, consider antibiotic lock therapy.

Candida species

An echinocandin is preferred for empirical therapy in patients who are critically ill; liposomal amphotericin B is an alternative therapy.
Antifungal susceptibility can be inferred from the species identification.
Repeat blood cultures on therapy until negative.
Remove catheters.
Dilated ophthalmologic examination on treatment to exclude endophthalmitis.

Treat for 14 d after first negative culture in uncomplicated infections.

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.
Credit to Dr David K. Warren.

When CVCs serve as the source of infection, treatment failure and relapse can occur without line removal for source control. Organisms on CVCs often form a slime-like biofilm, reducing their susceptibility to antimicrobial therapy and host defenses. This often necessitates the removal of the CVC for definitive treatment. However, the decision to remove the CVC can be difficult given the expense and risk involved, especially when patients may have limited options for vascular access. In general, CVCs should be removed in cases of soft tissue infection of the tunnel or the port reservoir, systemic complications (ie, septic shock, septic thromboembolic disease, endocarditis, osteomyelitis, or other metastatic foci of infection), infections caused *by S. aureus* or *Candida* species, and when prolonged bacteremia does not respond to appropriate antibiotic therapy. If salvage of the catheter is deemed necessary, there is evidence that the use of high-concentration antibiotic lock therapy may improve success rates. Consultation with an infectious disease specialist is recommended in complicated cases.

After removal of a central line guidelines recommend waiting 48 to 72 hours before replacement to ensure that the new line is not seeded from ongoing bacteremia. Additionally, any other catheters or indwelling devices should be evaluated for potential secondary sites of infection.

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Blood cultures drawn from central venous catheters or from peripheral venipuncture had similar positive and negative predictive values for detected bloodstream infection.

42 Invasive Fungal Infection

Patrick B. Mazi and Andrej Spec

Invasive fungal infections pose a serious threat to patients who are critically ill, causing high morbidity and mortality rates. While less common than bacterial infections, fungal infections are more severe, resulting in worse patient outcomes. Immune system dysfunction is the main risk factor for invasive fungal infections. Critical illness induced by factors such as infection, trauma, burns, surgery, malignancy, and exposure to immunosuppressive medications commonly causes compromised immunity in these patients. Early detection, accurate diagnosis, and prompt treatment with antifungal drugs and surgery are crucial for improving patient outcomes.

Fungi are ubiquitous environmental pathogens with varying incidences across the world. The overall incidence of invasive fungal infections peaked during the human immunodeficiency virus (HIV) epidemic. Incidence declined following the development of modern antiretroviral therapies but has increased again in recent years due to the expanded use of immunosuppressive therapies across various medical specialties. The increasing use and sometimes overuse of broad-spectrum antibiotics, increased utilization of long-term prosthetic devices (eg, ventricular-assist devices as destination therapy), and more aggressive surgical interventions also contribute to the rising incidence.

Clinically significant fungal infections are divided into three groups based on morphology: yeasts, dimorphic fungi, and monomorphic molds. While this classification does not represent a true phylogeny, it is the most useful approach for clinical and laboratory diagnosis. For instance, *Cryptococcus* and *Candida* are both classified as yeasts, even though *Cryptococcus* is more closely related to edible mushrooms than to *Candida.* However, both appear as round, budding yeast forms in clinical samples.

Candida spp. and *Cryptococcus* spp. are the most commonly encountered yeasts in clinical practice. *Pneumocystis jirovecii* is another pathogenic yeast that causes a multifocal pneumonia in immunocompromised hosts—classically seen in patients with advanced HIV.

The most common dimorphic fungi include *Blastomyces*, *Histoplasma*, *Coccidioides*, and *Penicillium.* Historically, this group of pathogens was called as “endemic fungi” because their distribution was geographically restricted. But due to increased travel and anthropogenic climate change, they are increasingly diagnosed outside of their traditional ranges. While identifying exposure to a classically endemic regimen remains an important diagnostic clue, a lack of geographic exposures does not rule out infection by this group of pathogens.

The most frequently isolated monomorphic molds are *Aspergillus* and the *Mucormycetes,* but there are over 200 clinically important species, each with complex and varied presentations. Due to variation in antifungal susceptibility, species-level identification is important for empiric antifungal selection while awaiting susceptibility testing.

Yeast

CANDIDA SPP.

Candida is a commensal organism found on the skin, in the gastrointestinal and genitourinary tract. While there are many species of *Candida,* only a few are commonly encountered in clinical care. The naming of *Candida* spp. has evolved with advancements in genomic testing, and health care providers should be aware of these changes. Examples include *Pichia kudriavzevii* (formerly *Candida krusei*) and *Nakaseomyces glabrata* (formerly *Candida glabrata*).

Overall, *Candida albicans* remains the most common species isolated from patients, accounting for 44% to 79.4% of infections.

This is beneficial because *C. albicans* is rarely resistant to commonly used antifungal medications. However, an epidemiologic shift toward non-albicans species—such as *C. glabrata* and *C. krusei—is* occurring, which has significant implications for empiric antifungal selection. *Candida krusei* is intrinsically fluconazole resistant, while *C. glabrata* may develop resistance to azoles and echinocandins after exposure. Although rare, azole and echinocandin-resistant *C. glabrata* isolates are exceedingly difficult to treat, requiring the use of amphotericin B. *Candida lusitaniae* is intrinsically resistant to amphotericin B but is rarely encountered and remains sensitive to azoles and echinocandins. *Candida parapsilosis* has been noted to have increased minimal inhibitory concentrations (MICs) to echinocandins. *Candida auris* is considered intrinsically multidrug resistant, especially to azoles and amphotericin B, with resistance reported in up to 35% of isolates.

Invasive candidiasis refers to the infection of normally sterile sites resulting from hematogenous spread or direct tissue invasion. It is important to note that *Candida* spp. are commonly isolated from the lungs and urine, but this is usually a result of colonization rather than true infection. However, colonization increases the risk of developing invasive candidiasis, which has an overall mortality rate exceeding 40%. The most common and clinically significant forms of invasive candidiasis in patients who are critically ill include candidemia, endocarditis, abdominal infections, and endophthalmitis (Table 42.1).

TABLE 42.1 Risk Factors for Invasive Candidiasis

Prolonged ICU stay
Candida colonization
Central venous catheterization
Broad-spectrum antimicrobials
Renal failure
Hemodialysis
Diabetes
Parenteral nutrition
Malignancy
Chemotherapy/immunosuppressive medications

Surgery (particularly abdominal)
Transplantation
APACHE II score ≥20
Acute pancreatitis

APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit.

The presence of *Candida* spp. in a blood culture warrants prompt investigation and initiation of empiric antifungal treatment. It should never be treated as a contaminant. However, blood cultures can only detect *Candida* bloodstream infections in 50% to 70% of patients, leading to the search for more reliable, nonculture-based diagnostic methods. One such method is the detection of 1,3-beta-D-glucan, a major component of fungal cell walls. This test has a sensitivity of 75% to 100% and a specificity of 88% to 100%, and is approved by the Food and Drug Administration (FDA). However, this broad-spectrum assay also detects other fungi, like *Aspergillus, Fusarium, Acremonium,* and *Saccharomyces* species, in addition to *Candida* spp. The positive results for 1,3-beta-D-glucan from most fungi severely limits its diagnostic utility. Currently, there are no alternative tests with adequate sensitivity and specificity to replace blood culture as the diagnostic gold standard.

Candida endocarditis is a severe manifestation of invasive candidiasis and is the most common cause of fungal endocarditis. It should be suspected with persistently positive blood cultures and can be confirmed with echocardiography, which frequently shows larger vegetations compared to those of bacterial endocarditis. *Candida* endocarditis is also more likely to embolize.

Endophthalmitis occurs in 2% to 26% of cases of candidemia and usually affects the choice of antifungal and the duration of therapy. Echinocandins are the preferred empiric antifungal class for candidemia but should not be used to treat endophthalmitis due to poor penetration into the vitreous. Azoles are preferred in this setting, and intravitreal antifungal injection may be considered. Uncomplicated candidemia requires 2 weeks of treatment, but the minimum treatment should be extended to 4 weeks in the presence of endophthalmitis. Due to the significant morbidity of

endophthalmitis, an early-dilated retinal examination by an ophthalmologist should be performed in all patients with visual changes or those unable to report visual changes (eg, intubated patients or those with altered mentation). A biopsy of a concerning lesion demonstrating characteristic histopathology can be considered definitive, but this is often not feasible in patients who are critically ill.

CRYPTOCOCCUS SPP.

Cryptococcus neoformans is the most common cause of cryptococcosis, while *Cryptococcus gattii* is the most common species in non–*C. neoformans* cases. Cryptococcal infection begins with the inhalation of infectious propagules. If the initial pulmonary infection is not cleared, hematogenous dissemination can occur. *Cryptococcus* tends to disseminate to melanin-rich regions like the central nervous system (CNS) and skin. Thus, the recovery of *Cryptococcus* outside the lungs likely represents disseminated disease and should be treated aggressively. Local inoculation can occur, though this scenario is rare and should not commonly be considered.

Cryptococcal infection should be suspected in any immunocompromised patient with fever, headache, and CNS symptoms. Conversely, any patient with known cryptococcal infection should be evaluated for underlying immunocompromising conditions, such as undiagnosed HIV, and for evidence of dissemination, including CNS disease, as this will significantly affect the treatment plan.

Cryptococcal meningoencephalitis is a common manifestation of cryptococcosis in intensive care unit (ICU) patients, especially patients with T-cell dysfunction such as patients living with HIV and solid-organ transplant recipients. In this population, it presents as subacute to chronic meningitis and patients often have several opportunities to be diagnosed earlier in the disease course. Later in the disease course, often when being evaluated in an ICU, patients often appear septic.

Definitive diagnose of cryptococcal meningoencephalitis requires lumbar puncture. Serial lumbar punctures have been shown to decrease mortality, even in patients with normal opening pressures. Cerebral spinal fluid (CSF) studies classically show lymphocytic pleocytosis, elevated protein, and elevated opening pressure. Diagnosis is confirmed by measuring the cryptococcal antigen in the CSF, which has high sensitivity (93%-100%) and specificity (93%-98%). False-positive tests can occur with infections caused by the fungus *Trichosporon asahii* or bacteria of the *Capnocytophaga* genera. Symptomatic patients should be treated with amphotericin B and flucytosine while evaluation for meningoencephalitis is underway. If further workup for dissemination is negative, patient may be deescalated to fluconazole.

The performance of serum cryptococcal antigen testing is comparable to CSF in patients with advanced HIV and suspected cryptococcal meningoencephalitis. Serum testing is only validated in patients with advanced HIV, though it can be considered in patients with other types of advanced immunosuppression or in patients who cannot undergo lumbar puncture. In this instance, a positive serum test supports a cryptococcal diagnosis, but negative testing is insufficient to rule out infection because patients without HIV often have a lower cryptococcal burden. Antigen titers generally correlate with cryptococcal burden in acute disease but should not be used to monitor the response to treatment. Antigen titers can remain elevated for months or even years and do not correlate with the clinical response to therapy.

Dimorphic Fungi

HISTOPLASMA

Histoplasma capsulatum is the most common dimorphic mycosis worldwide. Most infections are asymptomatic or self-limited, but some patients, predominantly those with T-cell dysfunction, can

develop acute pulmonary infections or severe and progressive disseminated infection.

Disseminated infection usually presents with fever, fatigue, hepatosplenomegaly, unintentional weight loss, and pancytopenia. Diarrhea and dyspnea are less common but may occur. Patients with advanced HIV or on immunosuppressive medications can present with overwhelming infection manifested by shock, respiratory distress, hepatic and renal failure, obtundation, and coagulopathy. Disseminated histoplasmosis is often confused with bacterial sepsis. Patients should be monitored for adrenal insufficiency (Waterhouse-Friderichsen syndrome), a rare but significant complication of disseminated histoplasmosis caused by direct infiltration of the organism into the adrenal glands. Fluid-refractory shock in patients with disseminated histoplasmosis should be treated with steroids.

In resource-rich settings, where early, aggressive treatment with amphotericin B is available, mortality is 10% to 25%. In resource-limited settings, mortality often reaches 50%.

For diagnosis, blood cultures along with urine and blood *Histoplasma* antigen testing should be performed in all patients suspected of having disseminated histoplasmosis. Serum *Histoplasma* serology can be helpful in cases of acute pulmonary histoplasmosis. Elevated lactate dehydrogenase (LDH), ferritin, alkaline phosphatase, and an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio greater than 2 are laboratory findings suggestive of histoplasmosis. Biopsy of a skin lesion, mucous membrane lesion, or bone marrow should be considered to confirm the diagnosis. Antigen testing may also be sent on CSF and bronchiolar lavage samples.

BLASTOMYCES SPP.

Blastomycosis is a systemic pyogranulomatous infection that develops after inhalation of aerosolized conidia. It is usually caused by *Blastomyces dermatitidis*, though several additional members of the genus have been recently identified, such as *Blastomyces gilchristii* and *Blastomyces helices*. Infection of the lungs is the most

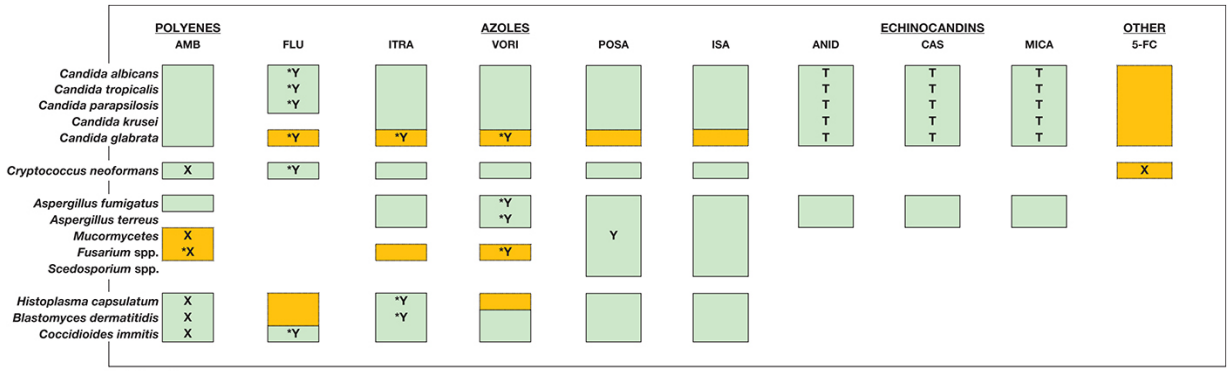
common, followed by infection of the skin, bones, brain, and genitourinary tract. Blastomycosis mortality is highly variable, though mortality from disseminated disease with multiorgan involvement can reach 90%.

Blastomycosis is frequently misdiagnosed, leading to a delay in treatment. Acute pulmonary infection is often mistaken for community-acquired bacterial or viral pneumonia. Blastomycosis, and other fungal infections, should be considered when patients fail appropriate courses of antibiotics for pneumonia. Chronic pulmonary blastomycosis is often initially thought to be malignancy or tuberculosis. Unlike other dimorphic mycoses, blastomycosis is not as strongly associated with immunocompromise. However, severe disease and dissemination are more common in immunocompromised patients.

Rarely, patients may present with diffuse pneumonitis associated with acute respiratory distress syndrome (ARDS). In small case series, the mortality rate associated with ARDS due to blastomycosis was over 50%, and most deaths occurred during the first few days of treatment. Blastomycosis should be considered in patients who have lived or traveled to areas with high rates of blastomycosis and later present with community-acquired ARDS.

Visualizing the *Blastomyces* on histology or isolation culture is required for definitive diagnosis. Serology is not useful for the diagnosis of blastomycosis. *Blastomyces* urine antigen testing has a sensitivity of 93%, but specificity is 79%. *Histoplasma* urine antigen is frequently positive in cases of disseminated blastomycosis due to antigen cross-reactivity. This can result in some diagnostic uncertainty and is often positive in cases of disseminated blastomycosis. Fortunately, histoplasmosis and blastomycosis are both treated with azoles (Table 42.2).

TABLE 42.2 Activity of Antifungal Agents



* = Preferred therapy
T= Initial therapy until species and/or sensitivity are known
X = Induction therapy if severe or disseminated infection
Y = Step-down therapy
Note: Fluconazole-sensitive *C. glabrata* can be treated with fluconazole 800 mg/d or voriconazole 200-300 mg twice a day.
AMB, amphotericin B; ANID, anidulafungin; CAS, caspofungin; 5-FC, flucytosine; FLU, fluconazole; ISA, isavuconazole; ITRA, itraconazole; MICA, micafungin; POSA, posaconazole; VORI, voriconazole.

COCCIDIOIDES SPP.

Coccidioides is hyperendemic to the deserts in southwestern US, Central, and South America. The risk of endemic exposure to *Coccidioides* spp. is approximately 3% per year. Primary *Coccidioides* infections manifest as community-acquired pneumonia, also known as Valley fever, which is usually self-limited but may be severe and require antifungal therapy. Hematogenous dissemination, predominantly in immunocompromised hosts, occurs to the skin, meninges, and bones. Coccidioidal meningitis should be suspected in patients with a persistent headache and fever after recent pneumonia.

Diagnoses are usually made using culture and histology, but serology is also helpful. Fluconazole is first-line therapy for coccidioidomycosis. Cases of meningitis in immunocompromised patients may require lifelong therapy, especially if the cause of immunocompromise cannot be reversed.

PENICILLIUM

Penicillium marneffei is an important cause of morbidity and mortality in patients living with HIV in hyperendemic regions of Southeast Asia. It typically presents as a syndrome similar to disseminated histoplasmosis or tuberculosis, with severe presentations that mimic bacterial sepsis.

Monomorphic Molds

Superficial skin and soft tissue infections, such as tinea corporis and onychomycosis, are the most common mold infections encountered in the ICU. Infection is usually caused by dermatophytes like *Trichophyton, Microsporum, and Epidermophyton* and rarely progress to invasive, life-threatening infection. However, these infections can cause skin barrier dysfunction and act as portals of entry for other more virulent pathogens. A classic example is disseminated *Fusarium* infection associated with onychomycosis in a neutropenic patient.

Aspergillus spp. are the most commonly encountered invasive molds. Only a few of the 200 or so species are pathogenic in humans, with *Aspergillus fumigatus, Aspergillus flavus,* and *Aspergillus niger* causing most infections. Other clinically significant molds include *Fusarium* spp. and *Scedosporium/Lomentospora,* as well as agents of mucormycosis, most commonly *Mucor* spp., *Rhizopus* spp., and *Rhizomucor* spp. These fungi are capable of causing a wide variety of infections. Some of these molds are more prone to certain syndromes (eg, *Fusarium* is most likely to cause disseminated cutaneous lesions, but most are able to cause the syndromes further listed down).

Most cases of disseminated infection occur in immunocompromised patients, particularly in stem-cell and solid-organ recipients. Other risk factors include diabetes and renal failure. The definitive diagnosis of invasive aspergillosis and other mold infections requires the isolation of the organism and identification of a host risk factor for invasive mold infection (Table 42.3). The performance of additional testing modalities, like serum galactomannan, is highly variable depending on both fungal pathogen and host characteristics. Reviewing recent literature is recommended when interpreting these tests.

TABLE 42.3 Risk Factors for Invasive Aspergillosis

Prolonged neutropenia (>10 d)
Hematopoietic stem-cell transplantation
Solid-organ transplantation
Corticosteroid/other immunosuppressive therapy
Advanced HIV
Chronic granulomatous disease

HIV, human immunodeficiency virus.

PNEUMONIA

Invasive pulmonary aspergillosis is the most common form of invasive fungal pneumonia, although other fungal pathogens can present similarly. For example, invasive fusariosis involves the lung in 50% of cases. Patients with invasive pulmonary aspergillosis classically present with the triad of fever, pleuritic chest pain, and dyspnea, usually in the setting of neutropenia. Imaging may show single or multiple nodules with or without cavitation, and a possible fungal ball creation.

The progression of the disease can lead to angioinvasion and dissemination, with a poor prognosis. Direct vascular invasion causes thrombosis and subsequent tissue infarction and necrosis. Patients at this stage usually have hemoptysis, which can be of large volume and life threatening. Such cases should undergo an emergent evaluation by interventional radiology for embolization and surgery for possible definitive surgical therapy.

RHINOSINUSITIS

Invasive fungal sinusitis is commonly caused by *Aspergillus* spp., Mucormycetes, and, to a lesser extent, *Fusarium.* However, dozens of other species can also cause invasive fungal sinusitis. The infection may be localized to the sinuses but can also invade adjacent tissues. Untreated infection will progress, eventually invading vasculature and/or brain tissue, leading to cavernous sinus thrombosis and a variety of CNS manifestations. MRI will show focal soft tissue lesions, focal bony erosions, or focal enhancement of the sinus lining. Invasive fungal sinusitis is a medical emergency, and

patients should undergo immediate surgical evaluation. Early, aggressive, and repeated debridement is the mainstay of treatment, in conjunction with a liposomal formulation of amphotericin B. Reconstitution of a patient's immune system is often necessary for a good outcome. Without it, poor outcomes are common, even with optimal medical and surgical interventions.

CUTANEOUS LESIONS

Cutaneous lesions mostly result from direct inoculation due to trauma, contiguous extension, or hematogenous spread. Cutaneous aspergillosis is most commonly seen in burn patients, transplant recipients, and individuals with hematologic malignancies. A skin biopsy is the definitive method for diagnosis.

Fusarium skin lesions in immunocompromised patients can present as either localized cellulitis or disseminated erythematous papular/nodular lesions with central necrosis. Mortality is very high in cases of disseminated disease, reaching up to 90% in persistently neutropenic populations. A new rash in persistently febrile, neutropenic patients should prompt consideration for fusariosis (Table 42.4).

TABLE 42.4 Indications/Dosing of Commonly Used Antifungal Agents

Agent	Dose	Dosing Adjustment Necessary
	Invasive candidiasis	
Fluconazole	400-800 mg/d, IV or PO	Renal insufficiency
Voriconazole	IV: 6 mg/kg every 12 h for two doses followed by 3-4 mg/kg every 12 h	Hepatic dysfunction IV vehicle may accumulate in renal insufficiency

Agent	Dose	Dosing Adjustment Necessary
	PO: <40 kg: 100 mg every 12 h. >40 kg: 200 mg every 12 h	
Caspofungin	70 mg loading dose followed by 50 mg/d, IV	Hepatic dysfunction
Anidulafungin	200 mg loading dose followed by 100 mg/d, IV	None
Amphotericin B deoxycholate[a]	0.6-1 mg/d, IV	None, careful monitoring renal and liver function
AmphotericinB lipid formulations[a] • Colloidal dispersion (Amphotec) • Lipid complex (Abelcet) • Liposomal (AmBisome)	3-5 mg/kg/d, IV	None, careful monitoring renal and liver function
	Invasive aspergillosis	
Itraconazole	IV: 200 mg every 12 h for four doses followed by 200 mg/d PO: 200-400 mg/d	Multiple drug interactions IV not recommended for CrCl <30 mL/min
Voriconazole	As listed above	As listed above
Isavuconazole	IV: 200 mg q8h × 6 (48 h), then 200 mg daily PO: 200 mg q8h × 6 (48 h), then 200 mg daily	

Agent	Dose	Dosing Adjustment Necessary
Amphotericin B deoxycholate[a]	1-1.5 mg/kg/d	As listed above
Amphotericin B lipid formulations[a]	5 mg/kg/d, IV	As listed above Higher doses sometimes used
Caspofungin	As listed above	As listed above
	Mucormycosis	
Amphotericin B deoxycholate[a]	1-1.5 mg/kg/d	As listed above
Amphotericin B lipid formulations[a]	≥5 mg/kg/d, IV[b]	As listed above Higher doses sometimes used
Isavuconazole	IV: 200 mg q8h × 6 (48 h), then 200 mg daily PO: 200 mg q8h × 6 (48 h), then 200 mg daily	

CrCl, creatine clearance; IV, intravenous; PO, by mouth.

[a]Bolus infusion of normal saline with dose recommended to decrease incidence of nephrotoxicity. Premedication with acetaminophen and diphenhydramine may decrease infusion-related reactions. In severe cases, hydrocortisone 50-100 mg IV may also be administered.

[b]Recommended start dose. Higher doses of 7.5-10 mg/kg/d are sometimes used, although there are no prospective trials of efficacy in zygomycosis.

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43 Infections in the Immunocompromised Host

Patrick B. Mazi and Stephen Y. Liang

Immunocompromised patients are at an increased risk for severe presentations of common community-acquired or nosocomial infections, as well as opportunistic infections (Table 43.1). The increased susceptibility to certain pathogens depends on the specific type, duration, and degree of the patient's immune defect. Immunologic defects can be generally categorized into impairment of the body's physical barriers, innate immunity, or adaptive immunity. Due to their increased risk of infection, immunocompromised patients often undergo recurrent exposure to antimicrobial therapy, either as prophylaxis or treatment, resulting in an increased incidence of infection with multidrug resistant pathogens. Intensivists can leverage an understanding of these factors to efficiently identify potential pathogens and implement optimal antimicrobial therapy.

TABLE 43.1 Common and Important Pathogens in the Immunocompromised Host

1. *Neutropenia*	
A. Pneumonia	Bacteria, *Aspergillus* spp., CMV, respiratory viruses
B. CNS infection	Bacteria, *Listeria monocytogenes*, *Aspergillus* spp., *Cryptococcus neoformans*, HSV, CMV, HHV-6
2. *Transplant*	
A. Pneumonia	Bacteria, *Nocardia* spp., *Mycobacterium tuberculosis*,

	nontuberculous mycobacteria, *Pneumocystis jirovecii*, *Aspergillus* spp., CMV, respiratory viruses, *Strongyloides stercoralis*
B. CNS infection	*Nocardia* spp., *L. monocytogenes, Aspergillus* spp., *C. neoformans*, dimorphic fungi, CMV, HHV-6, HSV, VZV, *Toxoplasma gondii*
3. *HIV*	
A. Pneumonia	
Any $CD4^+$	Bacteria, *M. tuberculosis*
$CD4^+ < 200$	Above + *P. jirovecii*, dimorphic mycoses, *T. gondii*
$CD4^+ < 50$	Above + *Mycobacterium avium complex*, CMV, VZV
B. CNS infection	
Any $CD4^+$	Bacteria, *L. monocytogenes*, HSV
$CD4^+ < 100$	*T. gondii*
$CD4^+ < 50$	*C. neoformans*, CMV, EBV-associated lymphoma, VZV, JC polyomavirus (PML)

CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; VZV, varicella-zoster virus.

Diagnosing infections in this population requires a high level of clinical suspicion. Classical signs and symptoms of infection (eg, fever, leukocytosis) are frequently absent in an immunocompromised host, risking delay or missed recognition of an infection. A muted inflammatory response may also disguise localizing symptoms (eg, abdominal pain, pulmonary infiltrates on chest radiography) and result in difficulty identifying an infectious focus. The diagnosis and

management of infectious complications in an immunocompromised patient can be challenging and are often best accomplished in consultation with an infectious disease specialist.

Immune System Function and Dysfunction

Physical and chemical barriers are the initial host defenses against infection. The skin uses tight junctions between cells of the epithelium to prevent the invasion of pathogens. Mucus covering mucosal tissues traps pathogens prior to invasion, and they are then cleared through various mechanical mechanisms (eg, mucociliary escalator of the respiratory tract, mechanical flushing of the urinary system). Stomach acid, lysozymes in tears and saliva, and antimicrobial peptides are examples of chemical defenses. While these host defenses are not frequently included in discussions on immunocompromised patients, they are critically important to assess when diagnosing and treating infections in patients who are critically ill. Dysfunction of one or more of these defenses can be the reason for intensive care unit (ICU) admission (eg, burns, exacerbation of cystic fibrosis). It is important to continually reassess patients for new barrier dysfunction developing during their admission, as new barrier dysfunction often serves as the portal of entry for infection in patients who are critically ill. Examples include skin breakdown from bedsores, endotracheal tubes inhibiting the mucociliary escalator, and cytotoxic chemotherapy causing compromise of mucosal tissues.

The innate immune system comprises neutrophils, macrophages, monocytes, natural killer (NK) cells, and the complement system. Nonspecific yet highly conserved pathogenic antigens (eg, lipopolysaccharide from the cell walls of gram-negative bacteria) bind to receptors on components of the innate immune system, triggering a pro-inflammatory signaling cascade. The innate immune system responds rapidly, within minutes to hours, and does not augment with repeated exposure to the same pathogen. In contrast, the adaptive immune system is highly specific to individual antigens

and is slow, taking days to develop. The specificity of the adaptive immune system is due to gene segment rearrangements in B and T lymphocytes, resulting in the expression of unique antigen receptors. Repeated exposure to the same pathogen results in the selection of B and T lymphocytes with the highest affinity receptors, thereby improving the immune response. Specific defects in innate or adaptive immunity lead to increased susceptibility to specific pathogens (eg, defects in the complement system result in susceptibility to *Streptococcus pneumoniae* and *Neisseria meningitidis*). Clinicians should possess a good understanding of immune defect-pathogen associations. Although an individual discussion of specific defects, associated pathogens, and the mechanism(s) implicated in increased susceptibility is beyond the scope of this chapter, the remainder of the chapter will discuss commonly encountered immunocompromised patient populations treated in the ICU.

Neutropenia

Neutropenia is commonly encountered in patients with primary hematologic malignancies, pre-engraftment hematopoietic stem cell transplant recipients, or those undergoing cytotoxic chemotherapy. Prolonged duration (>7 days) and severity of neutropenia increase the risk of bloodstream and other serious infectious complications. Severe neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3 or an anticipated decline to less than 500 cells/mm^3 over the next 48 hours. Severe neutropenia causes a muted host inflammatory response, and, as a result, fever is frequently the first and only sign of infection. Neutropenic fever is defined as a single temperature of 38.3 °C and more (101 °F) or a persistent temperature of 38.0 °C or more (100.4 °F) for more than 1 hour in a patient with severe neutropenia. More than half of all patients with neutropenic fever are ultimately found to have an established or occult infection. Neutropenic fever is a medical

emergency and should prompt the rapid administration of empiric antibiotic therapy and a workup for infectious etiology.

Infections common in the ICU—such as pneumonia, urinary tract infection, and bloodstream infection—are also the most common infectious etiologies in neutropenic fever. However, there are several additional diagnoses associated with neutropenia that intensivists should also consider. Chemotherapy-induced mucositis increases the risk for infections of the sinuses, oropharynx, and the gastrointestinal (GI) tract. Of these, the most feared is invasive fungal sinusitis due to its high morbidity and mortality (see Chapter 42, Invasive Fungal Infection). Neutropenic enterocolitis, also known as typhlitis, can manifest as a necrotizing infection of the cecum that can extend to the terminal ileum and ascending colon, leading to bowel perforation, peritonitis, hemorrhage, and sepsis. Inflammation of the GI tract can result in the translocation of intestinal bacteria across damaged mucosal membranes and can precipitate serious bloodstream infections with *Enterococcus* spp., *Candida* spp., Enterobacteriaceae, or other gram-negative organisms. Due to the severity of illness and prolonged hospital admissions, this population typically has exposure to repeated courses of broad-spectrum antibiotics and long-term vascular access (ie, central or peripherally inserted venous catheters). Repeated exposure to broad-spectrum antibiotics increases the risk of infection with multidrug-resistant organisms (MDROs) and *Clostridium difficile* infection (CDI). CDI may present as abdominal pain with diarrhea (see Chapter 45,*Clostridium difficile* and Other Infectious Causes of Diarrhea). Catheter-related infections associated with severe sepsis, suppurative thrombophlebitis, endocarditis, septic emboli, and bacteremia usually require catheter removal to clear the infection (see Chapter 41, Bacteremia and Catheter-Related Bloodstream Infections).

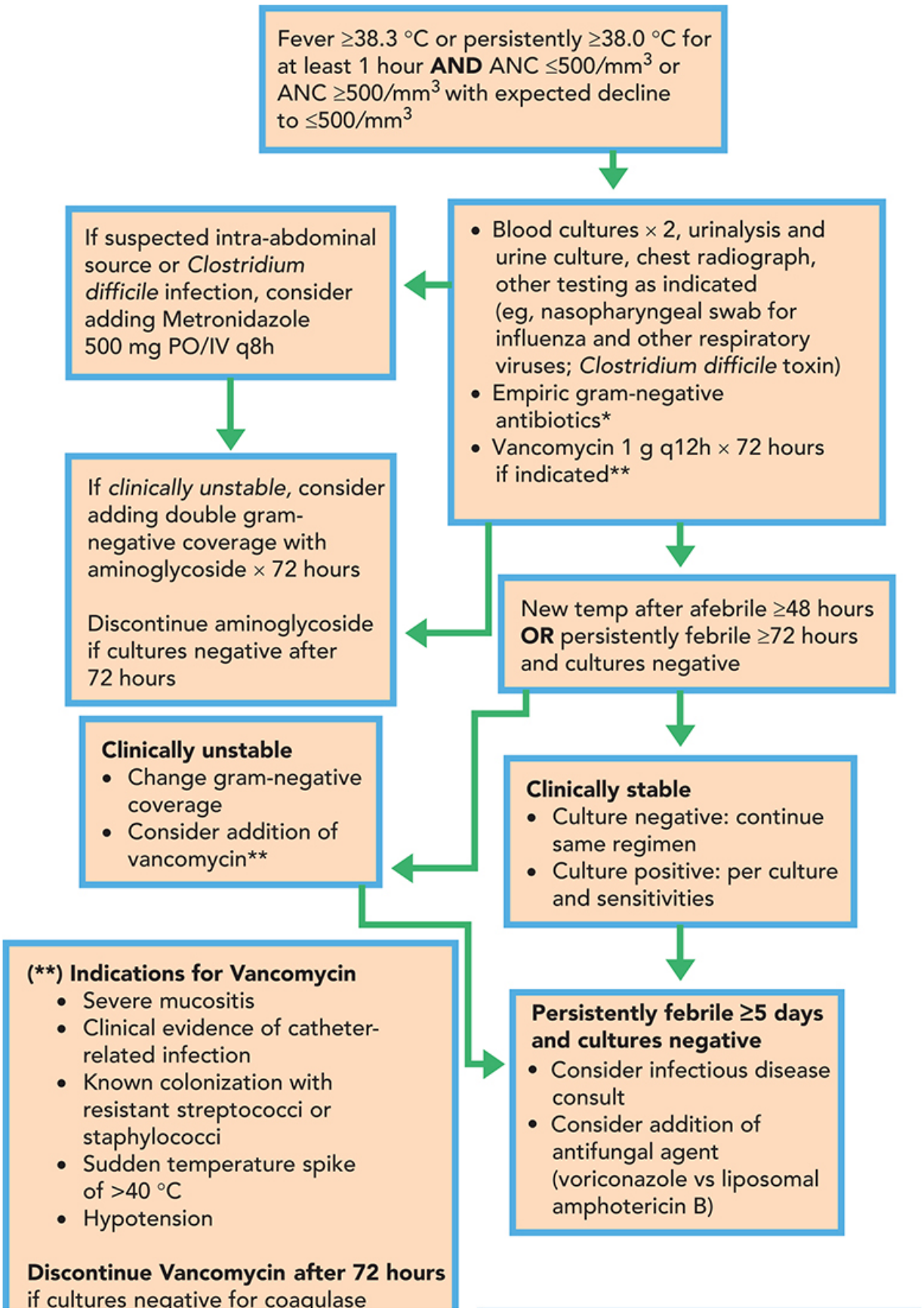
Over the last few decades, the continuum of pathogens implicated in neutropenic fever has shifted from gram-negative bacilli (*Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* species) toward gram-positive organisms (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp., and *Enterococcus*

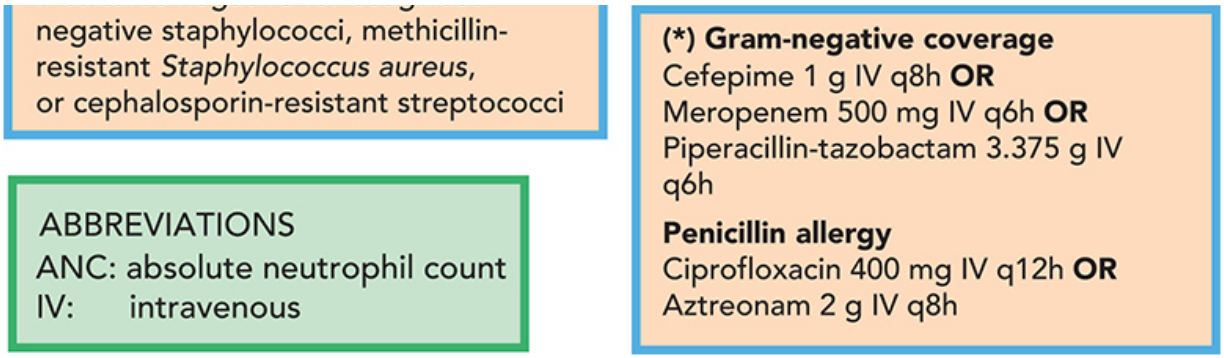
spp.). Prolonged, severe neutropenia is associated with an increased incidence of *Nocardia* and invasive fungal infection. *Candida* spp., *Aspergillus* spp., *Fusarium* spp., *Cryptococcus* spp., and the dimorphic mycoses (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis*) may be encountered. Disseminated candidiasis usually presents as a bloodstream infection, although hepatosplenic candidiasis is another notable presentation. Hepatic and splenic abscesses may be subtle (ie, microabscesses) and diffuse, making the radiographic detection of hepatosplenic candidiasis difficult. It is recommended to alert the reading radiologist if there is concern for this diagnosis. Reactivation of historical infections is also common in neutropenic hosts. Viral infections secondary to herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and human herpesvirus-6 (HHV-6) may assume a wide range of clinical manifestations, including meningitis, encephalitis, esophagitis, hepatitis, and skin disease. Reactivation disease should also be considered in patients with a prior history of tuberculosis.

Despite the epidemiologic shift away from gram-negative to gram-positive organisms, empiric antimicrobial coverage is recommended with broad-spectrum antimicrobial agents until infectious work-up is completed. Early (administered as soon as fever is recognized) empiric antimicrobial therapy in neutropenic fever decreases mortality and takes precedence once adequate blood cultures have been obtained. Based on local antimicrobial resistance patterns, monotherapy with an antipseudomonal cephalosporin, beta-lactam, or carbapenem for broad gram-negative coverage is initially recommended with or without vancomycin for gram-positive coverage (Algorithm 43.1). If blood cultures remain negative and a fever persists for more than 5 days, empiric antifungal therapy is usually warranted to cover mold infections. Empiric antiviral therapy is generally not recommended unless characteristic skin or cutaneous lesions suggestive of HSV or VZV are identified or active influenza or COVID-19 has been identified in the community. The ideal duration of antimicrobial therapy for neutropenic fever remains unsettled, particularly if no infectious etiology is identified. This is an

active area of research, and it is recommended to review the recent literature for new developments or engage with an infectious disease specialist.

ALGORITHM 43.1 Management of Neutropenic Fever


Fever ≥38.3 °C or persistently ≥38.0 °C for at least 1 hour **AND** ANC ≤500/mm^3 or ANC ≥500/mm^3 with expected decline to ≤500/mm^3
• Blood cultures × 2, urinalysis and urine culture, chest radiograph, other testing as indicated (eg, nasopharyngeal swab for influenza and other respiratory viruses; *Clostridium difficile* toxin)
• Empiric gram-negative antibiotics*
• Vancomycin 1 g q12h × 72 hours if indicated**
If suspected intra-abdominal source or *Clostridium difficile* infection, consider adding Metronidazole 500 mg PO/IV q8h
If *clinically unstable*, consider adding double gram-negative coverage with aminoglycoside × 72 hours
Discontinue aminoglycoside if cultures negative after 72 hours
New temp after afebrile ≥48 hours **OR** persistently febrile ≥72 hours and cultures negative
Clinically unstable
• Change gram-negative coverage
• Consider addition of vancomycin**
Clinically stable
• Culture negative: continue same regimen
• Culture positive: per culture and sensitivities
(**) Indications for Vancomycin
• Severe mucositis
• Clinical evidence of catheter-related infection
• Known colonization with resistant streptococci or staphylococci
• Sudden temperature spike of >40 °C
• Hypotension
Discontinue Vancomycin after 72 hours if cultures negative for coagulase
Persistently febrile ≥5 days and cultures negative
• Consider infectious disease consult
• Consider addition of antifungal agent (voriconazole vs liposomal amphotericin B)


negative staphylococci, methicillin-resistant *Staphylococcus aureus*, or cephalosporin-resistant streptococci
ABBREVIATIONS
ANC: absolute neutrophil count
IV: intravenous
(*) Gram-negative coverage
Cefepime 1 g IV q8h **OR**
Meropenem 500 mg IV q6h **OR**
Piperacillin-tazobactam 3.375 g IV q6h
Penicillin allergy
Ciprofloxacin 400 mg IV q12h **OR**
Aztreonam 2 g IV q8h

Adapted from Barnes-Jewish Hospital Stem Cell Transplant Unit Febrile Neutropenia Pathway.

Solid-Organ Transplantation

The spectrum of pathogens encountered in solid-organ transplantation (SOT) recipients is dynamic and changes over time. The risk for specific pathogens is affected by the organ transplanted, the time elapsed posttransplantation, and the degree of immunosuppression necessary to ensure graft survival (Table 43.2). Infectious risk is divided into early (<1 month posttransplant), intermediate (1-6 months posttransplant), and late (>6 months posttransplant). It is important to remember that this temporal grouping is arbitrary, and infectious risk exists as a spectrum. Any pathogen remains possible, even outside times when they are most common. During the first month following an SOT, infections are typically donor-derived, recipient-derived (ie, from colonization), or from nosocomial pathogens associated with the transplant surgery and/or prolonged hospitalization. Wound dehiscence, degradation of anatomic/anastomotic integrity, infected fluid collections (eg, blood, seroma, bile), and other infectious complications may be encountered depending on the type of graft (Table 43.3). The importance of early anatomic/anastomotic interrogation of the transplanted organ, early surgical debridement or drainage of infected tissue/fluid collections, and empiric antimicrobial therapy cannot be overemphasized. Hospital-acquired pneumonia, urinary tract infection, and infections of vascular catheters, surgical drains,

and other foreign objects are common during the early posttransplant period. Removal or exchange of any indwelling devices should be done in consultation with the surgical team and infectious disease specialists when a device-related infection is suspected. Reactivation of latent donor-derived or recipient-derived infections (eg, hepatitis B virus [HBV], CMV, tuberculosis, strongyloidiasis) may be encountered. Infection by colonizing (recipient-derived) or nosocomial bacteria and fungi is not uncommon. Due to recurrent antibiotic exposure and/or nosocomial acquisition, infections with multidrug-resistant organisms (methicillin-resistant *S. aureus* [MRSA], vancomycin-resistant enterococci [VRE], extended-spectrum beta-lactamase gram-negative organisms, and azole-resistant *Candida* species) are common, and empiric antimicrobial selection should reflect this potential. Although rare, infections transmitted to a transplant recipient from an infected donor organ must be considered in the setting of clinical deterioration during the first week after transplant, especially in the absence of an alternative diagnosis. Donor-derived infections with lymphocytic choriomeningitis virus (LCMV), West Nile virus, and other arboviruses, *Trypanosoma cruzi,* and *Toxoplasma gondii* are uncommon but are not usually detected with standard infectious work-up. When treating infectious complications of organ transplantation, it is vital to consider the drug-drug interactions of antimicrobials on serum levels of antirejection medications and adjust dosing accordingly.

TABLE 43.2 Timeline of Infections in the Solid-Organ Transplant Patient

≤1 mo	1-6 mo	≥6 mo
Postoperative complication and nosocomial infection • Surgical site infection • Graft ischemia/superinfection	**Postoperative complication (less common)** **Nosocomial infection**	**Low-level immunosuppression** • Community-acquired infection (pneumonia, UTI)

≤1 mo	1-6 mo	≥6 mo
• Anastomotic leak • Abscess/infected fluid collection • Pneumonia • Urinary tract infection • Catheter-associated infection • *Clostridium difficile* infection **Donor-derived infection** • *Aspergillus* spp., *Cryptococcus neoformans*, dimorphic fungi (*Histoplasma capsulatum, Coccidioides immitis*) • Herpesviruses (CMV, EBV, HSV, VZV, HHV-6), HIV, HBV, HCV, WNV, LCMV, rhabdovirus (rabies) • *Toxoplasma gondii, Trypanosoma cruzi* (Chagas) • *Balamuthia mandrillaris, Strongyloides stercoralis* **Recipient-derived infection** • *Mycobacterium tuberculosis* • *C. neoformans*, dimorphic fungi • Herpesviruses, HIV, HBV, HCV • *T. gondii, S. stercoralis* (hyperinfection)	**Opportunistic infection** (Depending upon antimicrobial prophylaxis) • *Listeria monocytogenes* • *Nocardia* spp. • *M.tuberculosis* • Nontuberculous mycobacteria • *Pneumocystis jirovecii* • *Aspergillus* spp. • *C. neoformans* • Dimorphic fungi • Herpesviruses (CMV, EBV, HSV, VZV, HHV-6/7/8) HBV, HCV Adenovirus Influenza, RSV Parvovirus B19 BK polyomavirus (nephropathy) *T. gondii* (myocarditis) • *Leishmania* • *T. cruzi* • Cryptosporidium • Microsporidium • *S. stercoralis* (hyperinfection)	• *Nocardia* spp. • *Rhodococcus* • *M. tuberculosis* • Nontuberculous mycobacteria • *Aspergillus* spp. • *Mucor* spp. • *C. neoformans* • Dimorphic fungi • Herpesviruses (CMV, EBV, HSV, VZV), EBV-related PTLD • HBV, HCV • JC polyomavirus (PML) • BK polyomavirus **High-level immunosuppression** • See Opportunistic Infection (1-6 mo)

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; PML,

progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disorder; RSV, respiratory syncytial virus; UTI, urinary tract infection; VZV, varicella-zoster virus; WNV, West Nile virus.
Adapted from Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357(25):2601-2614.

TABLE 43.3 Graft Site–Specific Infections

Heart	Myocarditis (*Toxoplasma gondii* seropositive donor to seronegative recipient) Mediastinitis/sternal wound infection (*Staphylococcus aureus*, *Staphylococcus epidermidis*)
Lung	Pneumonia (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *S. aureus*, *Burkholderia cepacia*, *Mycobacterium tuberculosis*, CMV, *Candida* species, *Aspergillus* species, *Scedosporium*/*Lomentospora*) Mediastinitis (*P. aeruginosa*, *E. coli*, *K. pneumoniae*, *S. epidermidis*)
Liver	Biloma/hepatic abscess/peritonitis (*Enterococcus*, *K. pneumoniae*, *Enterobacter cloacae*, *Candida* species)
Kidney	Urinary tract infection (*E. coli*, *E. cloacae*, *Klebsiella* species, *Proteus mirabilis*, *Enterococcus* species) Nephropathy (BK polyomavirus)

CMV, cytomegalovirus.

During the intermediate posttransplant period (1-6 months), immunosuppression is often at maximal levels, as extreme immunosuppression of peri-transplant induction therapy diminishes over time, and chronic immunosuppressive therapy is titrated to prevent acute transplant rejection. Infection with opportunistic pathogens is common during this period, and patients often require antimicrobial prophylaxis. Patients requiring treatment for acute rejection with high-dose corticosteroids and T-lymphocyte–depleting agents (antithymocyte globulins, OKT3, alemtuzumab) are especially vulnerable to opportunistic infections. Primary infection or reactivation of members of the Herpesviridae family is common,

especially in patients not on antiviral prophylaxis. CMV donor-recipient mismatch—donor (+) and recipient (-)—carries the highest risk of invasive CMV disease (pneumonitis, hepatitis, colitis). Coinfection with other immunomodulating viruses (CMV, EBV, HHV-6, HBV, hepatitis C virus [HCV]) may further predispose a patient to serious bacterial and fungal infections. Information concerning a patient's antimicrobial prophylaxis regimen, geographic location, occupation, hobbies, and epidemiologic exposures may lend further insight into the types of opportunistic infections possible.

As the risk of acute graft rejection declines over time, the requirement for immunosuppression generally stabilizes and decreases. By 6 months posttransplant, most patients are more likely to suffer from community-acquired infections (eg, pneumonia) rather than opportunistic infections. However, patients still requiring aggressive immunosuppressive regimens or those requiring treatment for acute rejection remain prone to opportunistic pathogens.

Hematopoietic Stem Cell Transplantation

In general, there is a higher risk of infection in allogeneic hematopoietic stem-cell transplant (HSCT) compared to autologous HSCT. The risk of infection after allogeneic HSCT is like that of the neutropenic patient, as these patients typically have periods of severe neutropenia. Similar to SOT recipients, posttransplant infectious risk can be separated into three general phases (Table 43.4). Patients undergoing autologous transplant share the same risks of infection during the pre-engraftment phase but largely recover immune function thereafter. The differential diagnosis for infection can be narrowed down by obtaining a focused medical history and conducting a physical examination assessing the type of transplant, the time elapsed since the transplant, the presence of chronic graft-versus-host disease (GVHD), immunosuppression therapy, antimicrobial prophylaxis, patient age, travel history, occupation, and hobbies.

TABLE 43.4 Timeline of Infections in the Hematopoietic Stem-Cell Transplant Patient

Pre-engraftment (<3 wk)	Early Post-engraftment (3 wk-3 mo)	Late Post-engraftment (>3 mo)
• Gram-positive bacteria (*Staphylococcus aureus*, coagulase-negative *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus*) • Gram-negative bacteria (*Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Stenotrophomonas maltophilia*) • *Clostridium difficile* • *Candida* spp. • *Aspergillus* spp. • *Fusarium* spp. • Mucormycetes • HSV (seropositive) • Respiratory viruses (RSV, parainfluenza, rhinovirus, influenza, adenovirus, human metapneumovirus)	• *Legionella pneumophila* • *Listeria monocytogenes* • *Nocardia* spp. • *Mycobacterium tuberculosis* • Nontuberculous mycobacteria • *Candida* spp. • *Aspergillus* spp. • *Fusarium* spp. • Mucormycetes • *Pneumocystis jirovecii* • CMV • EBV • HHV-6, -7 • VZV (seropositive) • Respiratory viruses • BK polyomavirus • *Toxoplasma gondii* • *Strongyloides stercoralis* • *Cryptosporidium*	• Encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*) • *Nocardia* spp. • Dimorphic mycoses • CMV • EBV • VZV (seropositive) • BK/JC polyomavirus • Parvovirus B19 • If chronic GVHD, then consider pre-engraftment and early post-engraftment organisms as well

CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HHV, human herpesvirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.
Adapted from Hiemenz JW. Management of infections complicating allogeneic hematopoietic stem cell transplantation. *Semin Hematol*. 2009;46(3):289-312.

The pre-engraftment phase lasts 3 to 4 weeks from transplant until neutrophil recovery. During pre-engraftment, HSCT recipients face high risk of gram-negative infections, associated with chemotherapy-related mucositis and the translocation of gut flora, as aforementioned. Gram-positive infections from skin and oropharyngeal flora are also common. Without an effective neutrophil response, bacterial infections can disseminate, leading to a rapidly fatal shock syndrome. Bacteremia, pneumonia, and CDI figure prominently during this phase. Seropositive recipients not taking antiviral prophylaxis are highly vulnerable to the reactivation of HSV and other herpes viruses, which can involve the skin, liver, and GI tract. Localized and disseminated azole-resistant candidiasis as well as invasive mold infections (*Aspergillus*, *Fusarium*, mucormycetes) presenting as pneumonia, sinusitis, central nervous system (CNS) infection, or skin lesions are also encountered. Invasive fungal infection is particularly worrisome during this period, because patient survival is often dependent on neutrophil count recovery, even in the setting of optimal antifungal therapy and surgical interventions. Finally, patients with delayed engraftment and prolonged neutropenia are at higher risk of invasive mold infections and *C. difficile* infections due to the use of broad-spectrum antimicrobials.

Bone marrow recovery marks the beginning of the immediate post-engraftment phase, typically lasting from 3 weeks to 3 months after transplantation. During this period, it is important to distinguish between infectious and noninfectious complications, as they occur in approximately equal numbers. GVHD and chemotherapy/conditioning regimen toxicities often present with symptoms similar to infections, such as pneumonia, diarrhea, cellulitis, and so on. Acute GVHD, when present, requires high-dose

immunosuppression that further increases the risk of infection. Although the risk of invasive fungal infections persists in the early post-engraftment period, it diminishes over time. Reactivation of immunomodulating human herpesviruses, most importantly CMV, can result in life-threatening conditions like pneumonia, encephalitis, colitis, and marrow suppression. While reactivation of toxoplasmosis is rare, intensivists should be aware of this potential diagnosis.

Six months posttransplantation, the recipient enters into the late post-engraftment phase. If a recipient has not developed GVHD, the immune system slowly returns to normal function within 1 to 2 years. Conversely, recipients with chronic GVHD remain at high risk of severe infections, especially those requiring additional immunosuppression for GVHD control. This population of patients remains susceptible to infections from encapsulated bacteria (*S. pneumoniae*, *Haemophilus influenzae*, and *N. meningitidis*), *Nocardia* species, fungi, and viruses (CMV, EBV, VZV, and adenovirus).

Human Immunodeficiency Virus

Modern antiretroviral therapy (ART), specifically the addition of protease and integrase inhibitors, has revolutionized the care of patients living with human immunodeficiency virus (HIV). Consistent adherence to ART results in the return of normal immune function in nearly all patients living with HIV (PLWH). In this population, admission to the ICU is rarely associated with HIV infection. ART should be continued in most patients while in the ICU. If there are concerns regarding inconsistent ART adherence, developing ART resistance, or drug-drug interactions, the decision to continue or restart ART should be made in collaboration with an infectious disease specialist. Patients with a new diagnosis or untreated HIV infection are more likely to present with acute infection requiring ICU admission. New HIV diagnosis should prompt screening for coexisting infections, as they may increase the risk of mortality (eg, hepatitis C).

The absolute $CD4^+$ lymphocyte cell count remains the standard lab test to stratify opportunistic infection risk in patients living with HIV. However, this test should be interpreted carefully in the acute setting because any significant change in total lymphocyte count can result in marked change in the absolute $CD4^+$ cell count. Medications, infection, or other medical diagnoses causing lymphocytosis or lymphopenia may falsely elevate or depress the absolute $CD4^+$ cell count. The absolute $CD4^+$ cell count in these settings often do not reflect the patient's true immune status. Interpretation of the $CD4^+$ percentage is often more useful for intensivists because the percentage of lymphocytes that are $CD4^+$ will remain roughly the same regardless of changes in the total lymphocyte count. A $CD4^+$ percentage less than 14% corresponds to an absolute $CD4^+$ lymphocyte cell count less than 200; patients below these thresholds have advanced HIV, and the remainder of this section addresses the infectious complications in this population. The term 'advanced HIV' is increasingly being used as preferred nomenclature in many medical settings due to stigma associated with the historical 'AIDS' terminology.

Pulmonary infection is common in patients with advanced HIV infection and has a broad differential diagnosis. Community-acquired pneumonia due to *S. pneumoniae*, *H. influenzae*, and increasingly *S. aureus* remains the most common causes of pulmonary infection, irrespective of $CD4^+$ cell count. *Mycobacterium tuberculosis* may present with pulmonary or extrapulmonary manifestations when combined with advanced HIV. The prevalence of *Pneumocystis jirovecii* pneumonia increases dramatically once the $CD4^+$ cell count drops below 200 cells/mm^3; the use of prophylactic antimicrobials does not exclude the diagnosis. In severe cases (when $PO_2 < 60$ and A-a gradient is >45), administration of adjunctive steroids has been associated with decreased mortality. Severe pulmonary manifestations of cryptococcosis, histoplasmosis, and other fungal pathogens occur commonly at $CD4^+$ cell count below 200 cells/mm^3. Advanced HIV increases the risk for disseminated mycobacterial infection, fungal disease, and bacteremia associated with

pneumonia. Pneumonia secondary to *Mycobacterium avium* complex (MAC), CMV, and VZV can occur below a $CD4^+$ cell count of 50 cells/mm^3. Adrenal insufficiency can complicate management and is associated with disseminated CMV, tuberculosis, histoplasmosis, Kaposi sarcoma, lymphoma, and treatment with pentamidine.

CNS infections are more common when the $CD4^+$ cell count is severely depressed. The risk of *T. gondii* encephalitis significantly increases as the $CD4^+$ cell count falls below 100 cells/mm^3. Symptoms of CNS toxoplasmosis include fever, headache, altered mental status, neurologic deficits, and seizures. In most cases, ring-enhancing lesions are seen on contrasted head computed tomography (CT) and/or magnetic resonance imaging (MRI). Less common infections associated with ring-enhancing lesions may include bacterial brain abscess, cryptococcomas, CNS fungal infections (eg, aspergillosis), and syphilitic gummas. Below a $CD4^+$ cell count of 50 cells/mm^3, meningoencephalitis secondary to *C. neoformans* may present with a severe headache, photophobia, and possibly coma, and is associated with markedly elevated intracranial pressures. In addition to antifungal therapy, serial lumbar punctures (even for patients with normal opening pressures) have been shown to decrease mortality in patients with cryptococcal meningitis. Herpesvirus encephalitis (HSV, CMV, and VZV), primary CNS lymphoma (EBV), and progressive multifocal leukoencephalopathy (JC polyomavirus) must be considered in patients with rapid neurologic deterioration and abnormalities on brain imaging.

Immune reconstitution inflammatory syndrome (IRIS) is a life-threatening complication of ART that can be indistinguishable from an acute opportunistic infection. Usually apparent within days to weeks of initiating ART, the rapid return of immune function leads to an exuberant inflammatory response against infectious agents that were previously clinically silent. *M. tuberculosis*, MAC, *P. jirovecii*, dimorphic fungi, and CMV infections are most common and may occur at new or previously known sites of infection. While corticosteroids may attenuate the inflammatory response, their use in IRIS remains controversial in many specific situations. Empiric

administration of corticosteroids is not broadly recommended, although it may be considered in specific cases (ie, IRIS associated with *P. jirovecii*).

Asplenia

Patients who have undergone splenectomy or are functionally asplenic due to underlying diseases (such as sickle cell disease, splenic artery thrombosis, malaria, infiltrative disease, complications of mononucleosis, or iatrogenic embolization for hemorrhage) face an increased risk of severe sepsis caused by encapsulated organisms, including *S. pneumonia*, *H. influenza*, and *N. meningitidis.* It is important to inquire about prior immunizations and immunize appropriately, as effective vaccines exist against each of these organisms.

Biologic Agents

Immunomodulating therapies are increasingly being used in the treatment of an ever-growing spectrum of medical conditions. Tumor necrosis factor (TNF) antagonists (eg, etanercept, infliximab, adalimumab) have found increased use in the treatment of rheumatoid arthritis, Crohn disease, and other inflammatory autoimmune disorders. Novel small molecule antineoplastic therapies (tyrosine kinase inhibitors, venetoclax, and others) and newer biologic agents such as rituximab, tocilizumab, abatacept, and tofacitinib are also growing in use. The infectious risks associated with these novel therapies remain unsettled and is an active area of ongoing research, and much of the data on newer agents is limited due to small study sample sizes. Despite this, some notable infection risks have emerged. For example, rituximab has received a black box warning for progressive multifocal leukoencephalopathy, and tofacitinib has been associated with an increased risk of HSV infection when combined with other therapies.

As TNF helps in regulating cell-mediated immunity, its inhibition can increase the risk of infection due to a range of viruses, fungi, protozoa, and intracellular bacteria. Risk factors for systemic infection include increased age, comorbidities, steroid use, concurrent use of disease-modifying antirheumatic drugs (DMARDs), previous use of DMARDs, functional status, and a previous history of systemic infections. Low-dose biologic agents do not increase the risk of infection compared to DMARDs alone. However, both standard and high-dose biologics, with or without DMARDs, increase the risk of infection. Of note, patients with untreated latent *M. tuberculosis* infection are susceptible to developing active disease after initiation of a TNF antagonist. Despite the attention given to reactivation of tuberculosis in this setting, invasive fungal infections, particularly histoplasmosis, are more common. Finally, infections due to opportunistic organisms (*T. gondii*, dimorphic fungi, *P. jirovecii*), *Legionella pneumophilia*, *Listeria monocytogenes*, *Nocardia*, actinomycetes, and nontuberculous mycobacteria are also possible.

SUGGESTED READINGS

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44 Infection Prevention in the Intensive Care Unit

Abby Sung and Jennie H. Kwon

Infections acquired in the intensive care unit (ICU) contribute significantly to morbidity and mortality, are associated with increased hospital length of stay, and can lead to costs exceeding $25,000 per occurrence. The cornerstone to preventing infections in the ICU is a multidisciplinary infection prevention program to implement effective interventions. Transmission-based precautions such as contact, droplet, and airborne should be instituted when indicated, and health care personnel (HCP) compliance should be a subject of continual process improvement. Contact Precautions (gown and gloves) should be instituted for those with antibiotic-resistant organisms, such as multidrug-resistant Gram-negative bacilli and *Clostridioides difficile.* Droplet Precautions (surgical mask) are necessary for large droplet infectious agents, such as influenza and meningococcus. Airborne Precautions (N95 respirator and negative pressure ventilation) are used for airborne infectious agents, such as *Mycobacterium tuberculosis* and varicella. To prevent HCP and patient exposure, transmission-based precautions must be instituted on first clinical suspicion. Infection prevention and/or occupational health should be consulted in cases in which a patient or HCP exposure may have taken place.

Health care–associated infections (HAIs) are infections patients can acquire while receiving medical treatment in hospitals, outpatient clinics, nursing homes, and other facilities where people receive health care. HAIs that are device associated, such as ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTIs), and central line–associated bloodstream

infections (CLABSIs), pose the greatest risk to ICU patients, where device utilization is higher than on the general wards.

The Centers for Disease Control and Prevention (CDC), Society of Healthcare Epidemiology (SHEA), and Infectious Diseases Society of America (IDSA) have published evidence-based guidelines for the prevention of device-associated infections. The recommendations for adult ICUs are discussed in this chapter and summarized in Tables 44.1 to 44.3.

TABLE 44.1 Summary of Recommendations for Preventing Ventilator-Associated Pneumonia (VAP) and/or Ventilator-Associated Events (VAEs) in Adult Patients

Essential practices to prevent VAP and other VAEs:

- Avoid intubation and prevent reintubation with the use of high-flow nasal oxygen or noninvasive positive pressure ventilation (NIPPV) as appropriate when safe and feasible.
- Minimize sedation whenever possible.
  - Preferentially use multimodal strategies and medications other than benzodiazepines to manage agitation.
  - Implement sedation minimization and ventilator liberation protocols.
- Evaluate ventilated patients for readiness to extubate daily unless medically contraindicated.
- Perform spontaneous breathing and awakening trials together to allow the patient the opportunity to pass the breathing trial and be extubated when they are maximally awake.
- Provide exercise and mobilization as early as possible to maintain or improve physical conditioning.
- Elevate the head of the bed by 30°-45°.
- Perform daily oral care with toothbrushing (without chlorhexidine).
- Provide early enteral rather than parenteral nutrition.
- Change the ventilator circuit when visibly soiled or malfunctioning (or per manufacturer instructions).
- Follow the Centers for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Council (HICPAC) guidelines for

sterilization and disinfection of respiratory care equipment.

Additional approaches to consider if VAP or VAE rates do not improve despite high compliance with essential practices

- Use selective oral or digestive decontamination in countries and ICUs with low prevalence of antibiotic-resistant organisms.
- Use endotracheal tubes with subglottic secretion drainage ports for patients expected to be mechanically ventilated for >48-72 h.
- Consider early tracheostomy (individualized for the patient's circumstances and preferences).
- Consider postpyloric rather than gastric feeding for patients with gastric intolerance or at high risk of aspiration.

ICU, intensive care unit.

Abbreviated and adapted from Klompas M, Branson R, Cawcutt K, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43(6):687-713.

TABLE 44.2 Summary of Recommendations for Preventing Catheter-Associated Urinary Tract Infections (CAUTIs) in Acute Care Hospitals

Basic practices to prevent CAUTI:

- Follow written policies, protocols, or guidelines on the use, insertion, maintenance, and removal of urinary catheters.
- Require that only trained staff be allowed to insert urinary catheters using aseptic technique and that the necessary sterile supplies, including sterile gloves, drape, sponges, antiseptic solution, and single-use lubricant, are readily available for use.
- Perform hand hygiene before donning sterile gloves for inserting the urinary catheter and before or after manipulating the catheter or site.
- Use the smallest-sized urinary catheter as feasible to minimize urethral trauma.
- Secure indwelling urinary catheters.
- Maintain a sterile, closed drainage system and replace the urinary catheter and drainage system if sterility is compromised (eg, system contaminated, seal broken, or leakage).

- Maintain unobstructed urine flow.
- Document the insertion, care, and removal of the urinary catheter. Daily assessment should include reason for continued use or document removal criteria that were met.
- Provide education and evaluate staff competency on proper insertion, care, and removal of urinary catheters to prevent CAUTIs.
- Insert urinary catheters only when necessary and remove as soon as there is no reason for continued use.
- Use intermittent catheterization instead of indwelling catheters, whenever possible.

Abbreviated and adapted from Lo E, Nicolle LE, Coffin SE, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* 2014;35(5):464-479.

TABLE 44.3 Summary of Recommendations for Preventing Central Line–Associated Bloodstream Infections (CLABSIs) in Adult Patients in Acute Care Hospitals

Before Insertion

- Provide an evidence-based indication for placement of the central venous catheter (CVC).
- Educate health care workers involved in placement and care of the CVC.
- Bathe ICU patients with chlorhexidine daily.

At Insertion

- Establish a process, such as a checklist, to ensure adherence to infection prevention practices.
- Perform hand hygiene before manipulating or inserting the CVC.
- The subclavian site is preferred to reduce infectious complications when a CVC is placed in the ICU setting.
- Utilize a cart or kit containing all supplies necessary for aseptic CVC insertion.
- Use ultrasound guidance when placing CVC in the internal jugular or femoral vein.
- Use maximum sterile barrier precautions during CVC insertion including mask, cap, sterile gown, and sterile gloves for HCP involved in CVC

insertion and cover the patient with a full-body drape.
- Prepare insertion site with an alcohol chlorhexidine solution containing at least 2% chlorhexidine gluconate.

After Insertion

- Ensure appropriate nurse-to-patient ratio and limit the use of float nurses.
- Use chlorhexidine-containing dressings for CVCs.
- Change transparent dressings on nontunneled CVCs and perform site care with a chlorhexidine-based antiseptic every 7 d or immediately if the dressing is soiled, loose, or damp.
- Disinfect injection ports, catheter hubs, and needleless connectors before accessing the catheter using an antiseptic (chlorhexidine/alcohol or 70% alcohol) and mechanical friction.
- Remove catheters that are no longer essential to the patient's care.
- Replace administration sets not used for blood, blood products, or lipid formulations at intervals up to 7 d.
- Perform surveillance for CLABSI.
- A CLABSI risk assessment should be conducted in areas with unacceptably high rates to ensure compliance with the above-mentioned prevention strategies before implementing additional approaches, such as antiseptic- or antimicrobial-impregnated catheters and dressings.

HCP, health care personnel; ICU, intensive care unit.

Abbreviated and adapted from Buetti N, Marschall J, Drees M, et al. Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43(5):1-17.

General Measures

Foremost in infection prevention is adequate hand hygiene before placing or handling an invasive device or examining a patient. Alcohol-based hand rubs (ABHRs) placed at the bedside increase compliance and preserve the skin integrity of HCP hands. ABHR can be used when hands are not visibly soiled, unless otherwise indicated by local infection prevention programs. Hand soaps should also be available for use when hands are soiled, following a body substance exposure, or other indications that are facility dependent

(such as after caring for a patient with *C. difficile*). Effective cleaning and disinfection of the ICU environment plays a key role in reducing the transmission of microorganisms, especially organisms such as *C. difficile* or *Candida auris.*

Commonly used invasive devices in the ICU allow organisms a portal of entry at a time when the patient is particularly susceptible to infection. These devices should be placed by trained HCP using appropriate aseptic technique. General infection prevention measures should include a daily review of the necessity of all invasive devices and removal of devices as soon as they are no longer clinically necessary. Additional prevention measures are aimed at the placement and maintenance of the device. For surgical ICUs, postoperative glycemic control is associated with a reduced risk of surgical site infections (SSIs).

The CDC's National Healthcare Safety Network (NHSN) is a nationwide HAI tracking system and provides standardized definitions for HAI surveillance. These surveillance definitions are used for reporting and quality improvement purposes and are different than clinical diagnosis. HAIs tracked by NHSN include CLABSI, CAUTI, ventilator-associated events (VAEs), SSI, multidrug-resistant organisms (MDROs), and *C. difficile*. Infection rates should be provided to ICU medical and nursing staff for review, and immediate action should be taken in times of increased rates. Surveillance of patient care outcomes and adherence to prevention measures should be monitored regularly for consistency. For optimal reduction in the transmission of infections, all evidence-based prevention methods for each infection must be applied together.

Catheter-Associated Urinary Tract Infection

An estimated 70% to 80% of urinary tract infections are attributable to an indwelling urethral catheter. Each day an indwelling urinary catheter remains, the patient has a 3% to 7% increased risk of CAUTI. Basic practice recommendations outlined in the SHEA and IDSA strategies for reducing CAUTIs should be adopted by all acute

care hospitals. Appropriate use of urinary catheters, utilization of external urinary collection devices, and prompt discontinuation when they are no longer medically necessary are paramount to preventing CAUTIs. Routine use of urinary catheters for incontinence or postoperative use without specific indications is not recommended. Placement should be performed after adequate hand hygiene, by a trained professional, and under aseptic technique and conditions. Catheter care should include maintenance of a closed drainage system and an unobstructed flow of urine. Should the integrity of the system be interrupted, the entire system should be replaced. All specimen collections should be performed aseptically.

Ventilator-Associated Pneumonia

Clinical surveys suggest that around 10% of ventilated patients develop nosocomial pneumonia. Recommendations to prevent VAP include measures to avoid intubation with the use of high-flow nasal oxygen or noninvasive positive pressure ventilation when feasible, prevent aspiration of secretions, prevent contamination of the ventilator circuit, minimize sedation, implement early mobilization, and perform daily assessment of readiness to extubate. Maintaining the head of the patient's bed at a minimum of 30° to 45° assists with preventing aspiration. Providing daily oral care with toothbrushing and preferentially providing early enteral rather than parenteral nutrition are associated with lower VAP rates and shorter ICU length of stay. Adult patients on mechanical ventilation are at risk for serious complications in addition to pneumonia, including barotrauma, acute respiratory distress syndrome, pneumothorax, pulmonary embolism, and pulmonary edema. Since a working surveillance definition for VAP is difficult to characterize, the CDC developed surveillance definitions for VAEs that include criteria for ventilator-associated conditions (VACs), infection-related ventilator-associated complications (IVACs), and possible ventilator-associated pneumonia (PVAP) as an alternative.

Central Line–Associated Bloodstream Infection

The risk for CLABSI in the ICU is high due to the prolonged use of multiple catheters that are frequently accessed. Recommendations to prevent bloodstream infections (BSIs) include placing the central venous catheter (CVC) using aseptic technique with maximal sterile barriers, including sterile gown, sterile gloves, mask, and cap. The patient should be covered with a full-body sterile drape. A chlorhexidine and alcohol solution is the preferred agent for skin antisepsis before CVC placement and dressing changes. The subclavian vein is associated with lower infection risk; however, the risks and benefits of infectious and noninfectious complications should be weighed on an individual basis. The use of a catheter insertion checklist and a standardized insertion kit to promote best practices is also recommended. The decision to use antimicrobial- or antiseptic-impregnated catheters, devices, dressings, or sponges should be made by the critical care and infection prevention team and based on an evaluation of current infection rates and compliance with evidence-based practices. Daily chlorhexidine bathing has been shown effective to prevent CLABSI in the ICU. Care should be taken to avoid CLABSI because the BSI can lead to other severe infectious complications, such as endocarditis, septic thrombophlebitis, and osteomyelitis.

Emerging Infectious Diseases

Emerging infectious diseases (EIDs) are infectious diseases that have newly appeared in a population (eg, COVID-19) or have existed but are rapidly increasing in incidence or geographic range (eg, Ebola, mpox). Infection prevention measures are critical to protect other patients in the ICU and the HCP caring for patients with EIDs and during epidemics or pandemics. Therefore, ICUs should have a preestablished preparedness plan, which includes formal staff training (with intermittent refresher training) on proper personal

protective equipment (PPE) use, a surge preparedness plan to ensure sufficient resources (such as PPE) and staff, and space allocation to care for these patients. As EIDs continue to emerge, Transmission-Based Precautions may evolve in response (eg, for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection, recommendations were based on specific PPE elements rather than a specific Transmission-Based Precaution label such as Airborne or Droplet).

Quality Improvement

Given the increased risk of HAI in the ICU setting, infection prevention surveillance and prompt action in response to increased rates are vital to patient care. There are multiple elements involved in a successful infection prevention program in the ICU, including written policies that reflect best practices, ensuring these policies are being performed, providing training to ICU staff, and conducting ongoing quality control and improvement measures. This complexity necessitates effective partnership with infection prevention specialists, ICU staff, and ICU leadership to improve patient outcomes in the ICU.

SUGGESTED READINGS

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45 *Clostridioides difficile* and Other Infectious Causes of Diarrhea

David Olafsson and Erik R. Dubberke

Diarrhea adversely impacts patients who are critically ill by contributing to dehydration, electrolyte imbalances, hemodynamic instability, malnutrition, and skin breakdown. The most common etiologies of infectious diarrhea among hospitalized adults in industrialized countries are *Clostridioides difficile*, with *Salmonella* spp., Norovirus, and Rotavirus, with *Cryptosporidium* in the immunocompromised host being less common.

Clostridioides difficile Infection

C. difficile is a spore-forming anaerobic bacillus that produces two exotoxins, toxin A and toxin B, which cause intestinal pathology. *C. difficile* is the leading cause of hospital-associated infectious diarrhea. However, most patients who acquire *C. difficile* remain asymptomatic, and approximately 10% of patients in the intensive care unit (ICU) are colonized with toxigenic *C. difficile*. Toxigenic *C. difficile* strains have the genes for toxin A and/or B. Most toxigenic strains produce both toxin A and B, although some strains produce only toxin B. Strains that produce only toxin B are capable of causing the same spectrum of illness as strains that produce both toxins; additionally, they are also capable of causing hospital-associated outbreaks. Nontoxigenic strains are nonpathogenic. The difference in ability to produce toxins is important from a diagnostic standpoint, as some diagnostics detect all strains of *C. difficile*, both toxigenic and nontoxigenic. This is discussed in more detail later.

Antimicrobial exposure is the most common and potentially modifiable risk factor for *C. difficile* infection (CDI), especially in the ICU, where patients are frequently on several antibiotic classes concurrently. Historically, the most common antibiotics associated with CDI have been clindamycin, fluoroquinolones, broad-spectrum cephalosporins, and ampicillin/amoxicillin. However, nearly all antibacterial agents can predispose patients to CDI. Patients can become symptomatic either during treatment or several weeks after antibiotics have been stopped. Other risk factors include increasing age, immunocompromised status, and severity of underlying illness. Although the mechanism is unclear, gastric acid suppressants such as H_2 antagonists and proton pump inhibitors are also associated with increased risk of CDI. The number of other patients with CDI in the same patient care area was found to be one of the factors most strongly associated with CDI. This provides additional evidence that CDI is caused from acquisition of *C. difficile* within the hospital setting and stresses the importance of preventing patient-to-patient transmission of *C. difficile.*

ASSESSMENT

Symptoms of CDI range from mild, self-limited diarrhea to life-threatening colitis. Ileitis has also been recognized in patients with CDI, though this is uncommon and typically seen in patients with a remote colectomy. Common symptoms of CDI include watery diarrhea, nausea, and abdominal pain or cramping. Although diarrhea is the hallmark for symptomatic CDI, severe abdominal pain and lack of diarrhea could indicate that the patient has ileus with toxic megacolon. About 30% of patients with CDI are febrile, and about 50% have leukocytosis. A white blood cell (WBC) count exceeding 20,000 may herald a patient at risk of rapid progression to fulminant colitis and septic shock.

DIAGNOSIS

It is important to differentiate between *C. difficile* carriage and CDI. CDI is primarily a clinical diagnosis with laboratory confirmation, and there is no direct test for CDI. Because all *C. difficile* diagnostic assays have the potential to detect asymptomatic *C. difficile* carriage, and given the high prevalence (approximately 10%) of asymptomatic carriers among ICU patients alongside common occurrences of diarrhea, careful patient selection is important to enhance the predictive value of diagnostic testing. *C. difficile* should be suspected in adults and children more than 2 years old with unexplained clinically significant diarrhea or if ileus is present in association with recent antibiotic use. Most commonly, a diagnosis of CDI is established with detection of *C. difficile* and/or its toxins in patients with diarrhea. The best method to diagnose CDI is not known. There are advantages and disadvantages to all available diagnostic assays, and results of testing must be correlated with the clinical picture. The clinician must be familiar with what testing is used at their facility and how best to interpret the results that are generated by those tests.

The most sensitive method to detect toxigenic *C. difficile* in stool is toxigenic culture. However, due to cost, labor, and prolonged turnaround time, it is rarely used for diagnostic purposes in the United States. The most sensitive method to detect *C. difficile* toxins in stool is cytotoxicity cell assays. Although considered the “gold standard” for detecting *C. difficile* toxins, this assay lacks standardization, and its performance can be impacted by the choice of cell line, the source of anti-toxin antibodies for neutralization, the type of control used, and reader interpretation. Owing to the transition to polymerase chain reaction (PCR)-based viral diagnostic assays, most clinical laboratories in the United States no longer have cell culture equipment necessary to perform cytotoxicity cell assays.

Currently available toxin enzyme immunoassays (EIAs) detect both toxin A and B, and their EIA results correlate with clinical outcomes. The primary concern of toxin EIAs is their lower analytical sensitivity compared to other *C. difficile* diagnostics. Despite this concern, they have an excellent negative predictive value of over 95% for CDI. EIAs that detect *C. difficile* glutamate dehydrogenase

(GDH), also known as common antigen, are highly sensitive in general, but are not specific for CDI. GDH EIAs will detect nontoxigenic *C. difficile* (strains that cannot cause CDI), and some non–*C. difficile* strains that also produce GDH. Also, owning to their high analytical sensitivity, GDH EIAs can detect asymptomatic colonization with toxigenic *C. difficile*. As such, these should always be performed in conjunction with an assay that detects *C. difficile* toxins. There are also PCR-based assays available for *C. difficile*, which typically detect toxin genes. These tests are rapid and have even higher analytical sensitivity than GDH EIAs and commonly detect asymptomatic toxigenic *C. difficile* carriage. Not surprisingly, the outcomes of patients with stool studies that are positive for *C. difficile* by PCR but negative for *C. difficile* toxins are similar to the outcomes of patients whose stool tests negative for *C. difficile* by PCR.

With those considerations in mind, several CDI guidelines have endorsed the use of multistep algorithms. Combinations include starting with a sensitive screen with a GDH EIA or PCR, and, if positive, followed by a toxin EIA. These approaches enhance the positive predictive value of the toxin EIA for CDI while maintaining a high negative predictive value as well. Some laboratories will do a GDH and toxin EIA, and if the results are discordant (ie, GDH positive, toxin negative) reflex to PCR. This approach takes advantage of the high negative predictive value of a negative PCR to rule out CDI. However, most patients who test positive by PCR do not have CDI. Therefore, this strategy provides limited useful information for ruling in CDI. For laboratories that use PCR as a standalone test, the positive predictive value for CDI is still only approximately 50%, even with careful patient selection for testing.

Patients with pseudomembranes at endoscopy should be presumed to have CDI, but this finding is neither sensitive nor specific. Only 50% of patients with CDI have pseudomembranes on endoscopy. Furthermore ischemic colitis and cytomegalovirus (CMV) colitis can also cause pseudomembranes.

TREATMENT

Supportive therapy with fluid and electrolyte repletion should always be provided. In addition, it is recommended to discontinue the offending antibiotic whenever possible, as this may reduce the risk of CDI recurrence. Empiric CDI treatment without confirmed diagnosis should only occur in the setting of fulminant infection, characterized by shock, ileus, or toxic megacolon.

Recent updates to treatment algorithms have simplified the differentiation between nonfulminant CDI and fulminant CDI (Table 45.1). In the 2021 focused update to the 2017 Infectious Disease Society of America (IDSA) CDI guidelines, fidaxomicin was identified as the preferred agent for both initial and recurrent CDI, if available. This recommendation was based on a pooled analysis of four randomized controlled trials (RCTs), suggesting an increased sustained response of CDI at 4 weeks compared with vancomycin. Fidaxomicin, a macrolide antibiotic, received U.S. Food and Drug Administration (FDA) approval in May 2011 for the treatment of CDI. It is minimally absorbed, extensively excreted in feces, exhibits a narrow spectrum of activity, is less disruptive to normal flora, and poses a lower risk of promoting bacterial resistance.

TABLE 45.1 IDSA/SHEA Guideline for the Management of CDI—2021 Update Recommended Treatment

Presentation	IDSA/SHEA Guideline for the Management of CDI—2021 Update Recommended Treatment
Initial CDI	Fidaxomicin 200 mg PO q12h for 10 d Vancomycin 125 mg PO q6h for 10 d
Fulminant CDI (hypotension, shock, ileus, or megacolon)	Vancomycin 500 mg PO/NGT q6h PO/NGT plus metronidazole 500 mg IV q8h Vancomycin 250 mg rectal retention enema q6h for ileus Surgical consult for possible subtotal colectomy

Presentation	IDSA/SHEA Guideline for the Management of CDI—2021 Update Recommended Treatment
First recurrence	Fidaxomicin 200 mg PO q12h for 10 d Fidaxomicin 200 mg PO q12h for 5 d then 200 mg q48h for 20 day Vancomycin taper: Week 1, 125 mg q6h; week 2, 125 mg q12h; week 3, 125 mg daily; week 4, 125 mg every other day; week 5-6, 125 mg every 3 d. Vancomycin pulse dosing: Up to 125-500 mg PO every 2-3 d for 3 wk Adjunctive treatment: One-time bezlotoxumab 10 mg/kg IV
Second recurrence	As for first recurrence Fecal microbiota transplantation

CDI, *Clostridioides difficile* infection; ISDA, Infectious Diseases Society of America; NGT, Nasogastric tube; PO, per os; SHEA, Society for Healthcare Epidemiology of America.

In the setting of fulminant CDI, it is recommended to administer both intravenous metronidazole and a higher dose of oral vancomycin (Table 45.1). There are no data indicating synergy between metronidazole and vancomycin, nor do data suggest that a higher dose of vancomycin is any better than the standard 125-mg dose (which achieves levels of vancomycin 500-1,000 times the MIC_{90} of *C. difficile* in stool). Rather, the rationale behind this recommendation is an attempt to get therapeutic antibiotics to the colon as quickly as possible. For patients with ileus, vancomycin retention enemas of 250 mg in 250 mL of normal saline, administered 4 times daily, should be considered. There is no prospective data to support the use of fidaxomicin in fulminant CDI, although fidaxomicin has been shown to be noninferior to oral vancomycin for initial treatment response in fulminant CDI. Furthermore, there is no evidence of synergy with metronidazole or oral vancomycin. As the main benefit of fidaxomicin lies in its sustained response after treatment is stopped owing to its narrow spectrum, there is no role for fidaxomicin when treating patients with

fulminant CDI who are also receiving metronidazole and oral and/or rectal vancomycin. Some patients with fulminant CDI have a biphasic illness, with initial improvement followed by subsequent deterioration. Colonic necrosis should be suspected in these patients, which may not be readily apparent on imaging.

Surgical consultation is recommended for patients with fulminant CDI as they may require a therapeutic subtotal colectomy. Subtotal colectomy is the established treatment for patients with septic shock, organ failure, megacolon, or organ perforation. Surgical interventions can benefit select patients, which may be identified by a rising WBC count (≥25,000) or a rising lactate (≥5 mmol/L). Diverting loop ileostomy and (antegrade) colonic vancomycin lavage may be a less invasive, colon-sparing surgical option. Antimicrobial treatment after total abdominal colectomy is highly individualized given limited published data to guide management. As such, treatment is tailored to individual patient scenarios (eg, clinical and pathologic evidence of ileal involvement, extent of surgery, and residual tissue). Consultation with an expert in infectious diseases is highly recommended.

Additional adjuncts in the setting for fulminant CDI have been described, all with variable results. Case reports and case series of tigecycline have described successes and failures. Intravenous immunoglobulin (IVIG) has been used as a salvage therapy in small retrospective studies and case reports in incidences of severe or recurrent CDI. Success rates of treatment have been variable across studies, which are limited by small sample sizes, differing treatment regimens, and potential confounding factors. If there is benefit, it is likely related to the immunomodulatory properties of IVIG and not the presence of anti–*C. difficile* toxin antibodies.

The authors of this chapter are not supportive of fecal microbiome transplantation (FMT)/live biotherapeutic products (LBPs) for fulminant CDI at this time. There are no placebo-controlled studies, and existing observational studies are hampered by continuation of CDI treatment antibiotics concurrent with FMT (and thus immediately kill the microbes in the FMT). Additionally, these studies often permit for an unlimited number of FMTs before declaring success. This

results in significant bias toward declaring positive results even when there may be no benefit (and possibly risk).

RECURRENCE

In general, about 20% of patients with an initial episode of CDI will have a recurrence, 45% of patients with one recurrence will have another recurrence, and more than 60% with at least two recurrences will have another recurrence. The recommended treatments for multiply recurrent CDI (defined as at least a third episode of CDI) include standard-dose fidaxomicin, tapered fidaxomicin, or tapered/pulsed-dose vancomycin with or without bezlotoxumab, as well as FMT/LBP (Table 45.1). The rationale for tapered regiments is that they give the colonic microbiota an opportunity to regenerate between spaced doses.

Bezlotoxumab is a fully human monoclonal antibody that binds *C. difficile* toxin B. Two phase 3 studies, MODIFY I and MODIFY II, demonstrated the effectiveness of bezlotoxumab in preventing recurrent disease after initial treatment with standard-of-care antibiotics. Patients treated with bezlotoxumab were significantly less likely to have CDI recurrence than the placebo group (17.4% vs 27.6%, P = .0003 for MODIFY I; 15.7% vs 25.7%, P = .0003 for MODIFY II). Bezlotoxumab was endorsed in the 2021 IDSA focused update for patients with recurrent CDI within 6 months of a prior episode.

For patients who have recurrent CDI despite multiple attempts at treatment, FMT/LBP can restore a normal microbiome to patients who have suffered significant disruption due to their normal flora via multiple courses of antibiotics and repeated episodes of CDI. The first ever FDA-approved LBP for prevention of recurrent CDI, Rebyota, has been available for prescription since February 2023. FMT/LBP should be considered in any patient with multiple recurrences of CDI but should be performed by an experienced treatment center. Of note, specialized approaches to prevent additional recurrences such as bezlotoxumab, FMT/LBP, prolonged tapers/pulses of vancomycin or fidaxomicin are typically not

indicated for patients who are critically ill. In fact, the opposite is likely true: these measures should be attempted after the patient has convalesced, optimizing the opportunity for success.

INFECTION PREVENTION AND CONTROL

The approaches to prevent CDI in the hospital aim to decrease risk of infection if *C. difficile* exposure occurs and prevent *C. difficile* transmission to other patients. The first line of defense against CDI is maintaining a healthy intestinal microbiota, making antimicrobial stewardship the mainstay of decreasing CDI. By decreasing the number of patients receiving antimicrobials and/or limiting high-risk antimicrobial exposures, the number of patients at risk for CDI is decreased. Up to 25% of antibiotic usage is not needed; this is true even in the ICU setting. Probiotics have failed to demonstrate efficacy in the primary and secondary prevention of CDI in randomized, placebo-controlled trials.

C. difficile transmission is through the fecal-oral route. Infected patients can excrete large numbers of spores in feces. These resistant spores contaminate the hands of health care workers, bedding, medical equipment, and other structures in the patient's room and unit. Hand contamination can occur even when the patient is not touched. Strategies to interrupt transmission involve using contact precautions, signage, and rigorous environmental cleaning. Even though alcohol does not kill *C. difficile* spores, it is not recommended to preferentially perform hand washing with soap and water over alcohol-based foams/gels after caring for patients with CDI in nonoutbreak settings. Numerous studies have failed to demonstrate an increase in CDI with the use of alcohol-based hand hygiene products or decreases with soap and water. This is likely due to multiple factors including extremely poor adherence to hand hygiene when soap and water is the preferred method, the efficacy of gloves in preventing contamination of hands, and potential for contamination of hands after removing gloves if the sink used to wash hands is the same sink used by the patient.

New approaches to preventing CDI are being investigated, but existing data are not supportive of adoption outside of a study at this time. One approach includes screening patients for *C. difficile* carriage on admission to the ICU and placing those identified as *C. difficile* carriers on contact precautions. However, there are significant hurdles to screen for *C. difficile* in an effective and timely manner. Rectal swab PCR has a sensitivity for asymptomatic carriage below 75% compared to stool culture. In addition, a post hoc analysis of a cluster randomized trial comparing the standard practice for glove and gown use versus the intervention to require all health care workers to wear gloves and gowns for all contact with the patient or patient's environment failed to demonstrate a reduction in *C. difficile* acquisition in the intervention ICUs. Another approach that should be used sparingly at this time is oral vancomycin prophylaxis. Oral vancomycin is likely effective at preventing CDI, but it is highly disruptive to the microbiome, causing additional disruption beyond the other antibiotics the patient is receiving. This will enhance selective pressures for other antibiotic-resistant organisms and may increase the risk for CDI once it is stopped.

Non–*Clostridioides difficile* Infectious Diarrhea

Most diarrhea in hospitalized patients is noninfectious. However, it is essential to consider an infectious etiology in an ICU patient when they have the following symptoms: three or more watery bowel movements per day, blood, or mucus in the stool, vomiting, severe abdominal pain, and/or fever. Establishing the etiology of infectious diarrhea is important, so pathogen-specific treatment can be initiated (if available) and the appropriate precautions can be taken to prevent transmission to other patients. It is important to obtain history of potential risk factors for disease acquisition and severity, including recent antibiotic use, type of food consumed, ingestion of untreated water, recent travel, contact with animals and family members who are ill, liver disease, immunosuppression due to human immunodeficiency virus (HIV) or chemotherapy, sexual practices,

asplenia, sickle cell disease, and residence in a nursing home in the past 30 days. It is also important to be cognizant that some etiologies of infectious diarrhea occur seasonally, such as norovirus, because hospital outbreaks are typically coincident with those in the community. The fecal-oral route is the usual mode of infection, and person-to-person spread is the most common form of transmission. It is important to work with Infectious Diseases and Infection Prevention personnel to implement appropriate measures to halt the spread of the causative organism to other patients and staff in the ICU.

Etiologic diagnosis of infectious diarrhea is generally based on stool cultures, nucleic acid amplification tests, antigen testing, and/or direct microscopy depending on the pathogen and diagnostics available (Table 45.2). It is important to differentiate between hospital-acquired diarrhea and community-acquired diarrhea, as well as host characteristics, in selecting the right diagnostic test. A broader differential is warranted for immunodeficient hosts and community-onset diarrhea with consideration for further viral and parasitic workup. Non–*C. difficile* enteropathogenic bacteria and parasites are detected in less than 1% of patients with diarrhea who have been hospitalized for more than 3 days. A modified "3-day rule" has therefore been proposed to guide when to culture stool for enteropathogenic bacteria other than *C. difficile.* The rule states that stool cultures sent more than 72 hours after admission for diarrhea should be rejected unless one of the following are present: neutropenia ($<0.5 \times 10^6$ cells/mL), HIV infection, suspected nondiarrheal manifestation of enteric infection (erythema nodosum, mesenteric lymphadenitis, polyarthritis, or fever of unknown origin), patient age of more than 65 years with comorbidities causing end-organ damage, or a suspected hospital-acquired outbreak. This rule is a safe and cost-effective cut-off for rejecting stool samples of adult patients.

TABLE 45.2 Other Noteworthy Causes of Infectious Diarrhea Found in the ICU

Organism	Laboratory Diagnosis	Treatment: First Choice (Second Choice)
Salmonella spp.	Stool culture, blood culture, NAAT	Non-typhi: Supportive (ceftriaxone or ciprofloxacin) Typhi: Ceftriaxone or ciprofloxacin (ampicillin, TMP-SMX, or azithromycin)
Campylobacter	Stool culture, NAAT	Azithromycin (ciprofloxacin)
Shigella	Stool culture, NAAT	Azithromycin, ciprofloxacin, or ceftriaxone (ampicillin or TMP-SMX)
STEC	Stool culture for O157:H7, Shiga toxin NAAT or immunoassay	Supportive, avoid antibiotics
Yersinia enterocolitica	Specialized stool culture	TMP-SMX (ciprofloxacin or cefotaxime)
Vibrio cholera	Stool culture, NAAT	Oral rehydration therapy, doxycycline (ciprofloxacin, azithromycin, or ceftriaxone)
Norovirus	NAAT	Supportive (prevent spread)
CMV	Biopsy with immunohistochemistry	Ganciclovir/valganciclovir therapy, with reduction of iatrogenic immune suppression if applicable.
Giardia	EIA, NAAT	Tinidazole or nitazoxanide (metronidazole)

Organism	Laboratory Diagnosis	Treatment: First Choice (Second Choice)
Cryptosporidium	DFA, EIA, NAAT	Immunocompetent-no HIV: nitazoxanide 500 mg PO bid × 3 d HIV-effective antiretrovirals; nitazoxanide not licensed for immunodeficient patients

CMV, cytomegalovirus; DFA, direct fluorescent antibody test; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test; PO, per os; STEC, Shiga toxin–producing *E. coli;* TMP-SMX, trimethoprim-sulfamethoxazole.

Stool cultures or PCR for enteropathogenic bacteria (*Salmonella, Shigella*, Shiga toxin–producing *E. coli* [STEC], *Campylobacter*, and *Yersinia*) are warranted in patients presenting with diarrhea and signs of hemodynamic compromise, abdominal pain/tenderness, bloody/mucoid stools, and/or fever. It is worth noting that many patients presenting with enteric infection from STEC are not febrile on presentation, and painful bloody diarrhea in the absence of fever should raise suspicion. Patients suspected of having STEC should have a blood smear to evaluate for schistocytes, along with close monitoring of cell counts and renal indices to watch for hemolytic uremic syndrome (HUS). Blood cultures should be obtained in patients presenting with sepsis, immunocompromised patients, and febrile patients with epidemiologic exposures to enteric pathogens. Multipathogen nucleic acid amplification test panels are increasingly being used in clinical practice. However, it is important to consider the clinical context in which the sample was obtained when interpreting the results of those tests, as they may reflect nonpathogenic colonization or nonviable organisms. Further imaging tests can be helpful in the diagnosis of extraintestinal complications of enteric infections and may suggest specific etiologies (eg, aortitis in invasive salmonellosis and yersiniosis). For patients presenting with proctocolitis, a history of receptive anal sex and testing for sexually transmitted infections should be sought (eg, syphilis, gonorrhea, chlamydia, herpes, and monkeypox). Endoscopic

evaluation can be helpful in certain cases. In particular, it is worth noting that the diagnosis of CMV gastrointestinal (GI) disease (eg, CMV colitis) is based on immunohistochemistry findings. A negative CMV PCR test on peripheral blood should not be used alone to exclude CMV GI disease in a compatible clinical scenario, as not all patients have detectable viremia.

As a general rule, empiric treatment for enteropathogenic bacteria is not indicated, except in the setting of severe symptoms and/or immunocompromise. In ideal circumstances, treatment should be deferred until a pathogen has been isolated, and consideration of host characteristics should be taken into account (Table 45.2). For the scope of this manual, however, empiric treatment is often indicated with broad-spectrum antimicrobials (eg, ceftriaxone or cefepime), with further adjustments made as diagnostic results become available. Highly suspected or confirmed infections with Shiga toxin–producing organisms (eg, STEC) should not be treated with antimicrobials (beta-lactams, trimethoprim/sulfamethoxazole, metronidazole, or fluoroquinolones) due to observational data suggesting harm rather than benefit. This is thought to be due to increased toxin release and increased risk of HUS.

It is particularly important to diagnose norovirus infection because of its short incubation period of 24 hours and its potential for rapid dissemination in hospitals to patients and health care workers, causing large economic loss and morbidity. The signs and symptoms of norovirus are nonspecific. Therefore, a specific diagnosis requires laboratory confirmation, which can now be achieved through commercially available PCR-based diagnostics. Norovirus is transmitted by feces and/or vomitus, and patients should be placed in contact precautions throughout the duration of their illness. Special attention to environmental cleaning is needed, even if surfaces do not appear to be soiled. Aerosolization may occur as a mode of infection, so those directly exposed to emesis, potentially aerosolizing events, or engaged in cleaning heavily infected areas should wear masks. Although norovirus is relatively resistant to alcohol, there is no evidence that alcohol-based hand hygiene products are ineffective for hand decontamination. Norovirus has

been associated with pseudo-outbreaks of *C. difficile* due to more frequent testing for *C. difficile* and detection of asymptomatic *C. difficile* colonization in patients with diarrhea due to norovirus. Treatment is supportive in nature.

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46 COVID-19 and Other Viral Pneumonias

Kevin D. Betthauser and Tej M. Patel

Viral pneumonia is a leading cause of hospitalization, critical illness, and health care resource utilization worldwide. While the prevalence of viral pneumonia in the intensive care unit (ICU) is unknown, data have described an increasing incidence in the context of advancements in testing and diagnosis of community-acquired, hospital-acquired, and ventilator-associated viral pneumonia. Viral pathogen(s) encountered by critical care providers vary by geography, season, and other ecologic, environmental, or host factors; however, pathogens may include picornaviruses (rhinovirus, enterovirus), coronaviruses (including severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), respiratory syncytial virus (RSV), influenza viruses, metapneumovirus (MPV), parainfluenza viruses, and adenoviruses. The clinical manifestations and associated complications of viral pneumonias vary greatly. These include but are not limited to asymptomatic infection, viral reactivation, acute respiratory distress syndrome (ARDS), septic shock, chronic obstructive pulmonary disorder (COPD) or asthma exacerbation, acute decompensated heart failure, thromboembolism, and bacterial/fungal superinfection. Furthermore, assessment of long-term sequelae of viral pneumonias (eg, post-acute COVID-19 syndrome [PACS], also known as “long COVID”) remains a growing area of research.

The increasing incidence of viral pneumonia, the growing at-risk populations, recent epidemics, and a pandemic, along with novel preventive and treatment options for viral pathogens, highlight the importance of understanding appropriate management. Effective prevention strategies, including vaccination and infection control

measures, early identification and isolation of infected patients, aggressive supportive care, and the use of antiviral therapies, are crucial in reducing the burden of viral pneumonias in the ICU.

The objective of this chapter is to review the medical management of viral pneumonia in patients who are critically ill. The relevance and treatment of associated topics, including viral reactivation and viral tracheobronchitis, are not discussed. The focus is on the role of antiviral medications in the treatment of influenza and SARS-CoV-2 in patients who are critically ill. Readers are referred to other references or chapters of this manual for details on the management of non–critically ill viral pneumonia and complications associated with viral pneumonia (septic shock, acute respiratory failure, ARDS, acute liver failure, etc).

Preventive and Supportive Measures

Ubiquitous to the management and prevention of viral pneumonia is the implementation of appropriate infection control measures. The mode of viral transmission will dictate necessary infection control precautions, including patient isolation and the use of personal protective equipment. This may include various combinations of droplet, contact, and/or airborne precautions. Critical care practitioners must be cognizant that appropriate measures are taken during all patient care activities, including procedures likely to result in aerosol production (eg, bronchoscopy). In addition, the importance of appropriate hand hygiene and cleaning/decontamination processes cannot be understated in preventing viral transmission in the ICU. The most effective method of viral pneumonia prevention remains vaccination. Provided the potential for immune dysregulation and adverse reactions, routine vaccination of patients in the ICU against viral pathogens remains controversial and will not be the focus of this chapter. Still, critical care providers should screen all patients for vaccine eligibility and consider administration upon clinical improvement or at various transitions of care.

Various supportive measures to facilitate the recovery of viral pneumonia may be employed by ICU practitioners, as summarized in Table 46.1. With limited and mixed data to support the routine use of all measures, the need to initiate or discontinue these interventions should be dictated by the clinical situation of each patient. Nonetheless, ongoing assessment of the efficacy and safety of these interventions is crucial for managing patients with viral pneumonia. Readers are referred to other references or chapters of this manual for further discussion and direction regarding these interventions in the context of critical illness.

TABLE 46.1 Supportive Care Measures in the Management of Viral Pneumonia

Antipyretics (eg, acetaminophen)	Intravenous fluid replacement
Bronchodilators (eg, albuterol)	Invasive mechanical ventilation
Electrolyte replacement	Supplemental oxygen/noninvasive mechanical ventilation
Extracorporeal membrane oxygenation	Sleep hygiene
Intravenous fluid replacement	Venous thromboembolism prophylaxis

Management of Influenza Viruses

In addition to supportive care measures, antiviral medications targeting various stages of the viral life cycle are commercially available (Table 46.2). The routine use of M2 ion channel inhibitors, such as amantadine and rimantadine, is not recommended due to their lack of activity against influenza B and high rates of resistance (>90%). Neuraminidase inhibitors (NAIs), namely oseltamivir, remain the mainstay of treatment for patients who are critically ill with

influenza A/B pneumonia. Associations between early oseltamivir administration and improved outcomes are consistent with its mechanism of action. Combined with its reasonable safety profile, ICU providers should strongly consider using oseltamivir for all patients presenting with influenza pneumonia, particularly if early in their disease course. Current data do not support the routine use of a high dose (eg, 150 mg), extended duration (eg, 10 days), or test-driven duration strategy of oseltamivir in critical illness. However, severely ill and/or immunocompromised patients represent populations of interest in these areas. Two other NAIs, zanamivir and peramivir, are used infrequently in the ICU setting due to limited data and/or safety concerns. Peramivir may be a reasonable alternative to oseltamivir in patients with influenza unable to tolerate or absorb oral/enteral oseltamivir. Baloxavir represents the first Food and Drug Administration (FDA)–approved cap-dependent endonuclease inhibitor targeting influenza A and B. Data regarding the efficacy of baloxavir for hospitalized patients remain limited; however, treatment may be considered for patients with a documented allergy or intolerance to NAIs or suspected NAI resistance. In severely ill or highly immunocompromised patients, combination therapy with baloxavir and oseltamivir or peramivir may be considered.

TABLE 46.2 Available Antiviral Medications Targeting Influenza Virus(es)

Medication	Class/Mechanism	Typical Dosing and Administration	Adverse Effects
Amantadine[a]	M2 ion channel inhibitor	100 mg PO/PT Q12 h[b]	CNS effects, orthostatic hypotension
Rimantadine[a]		100 mg PO/PT Q12 h[b]	

Medication	Class/Mechanism	Typical Dosing and Administration	Adverse Effects
Oseltamivir	Neuraminidase inhibitor	75-150 mg PO/PT Q12-Q48 h[c]	Nausea, vomiting, CNS effects, skin reactions (peramivir), avoid in airway disease (zanamivir)
Peramivir		100-600 mg IV[c,d]	
Zanamivir		10 mg INH Q12 h	
Baloxavir	Polymerase inhibitor[e]	40-80 mg PO/PT once	Nausea, vomiting, diarrhea

CNS, central nervous system; INH, inhaled; IV, intravenous; PO, by mouth; PT, per tube.

[a]No influenza B activity. Use not recommended due to high rates of resistance.

[b]Dose adjustments for renal and hepatic dysfunction required.

[c]Dose adjustments for renal dysfunction required.

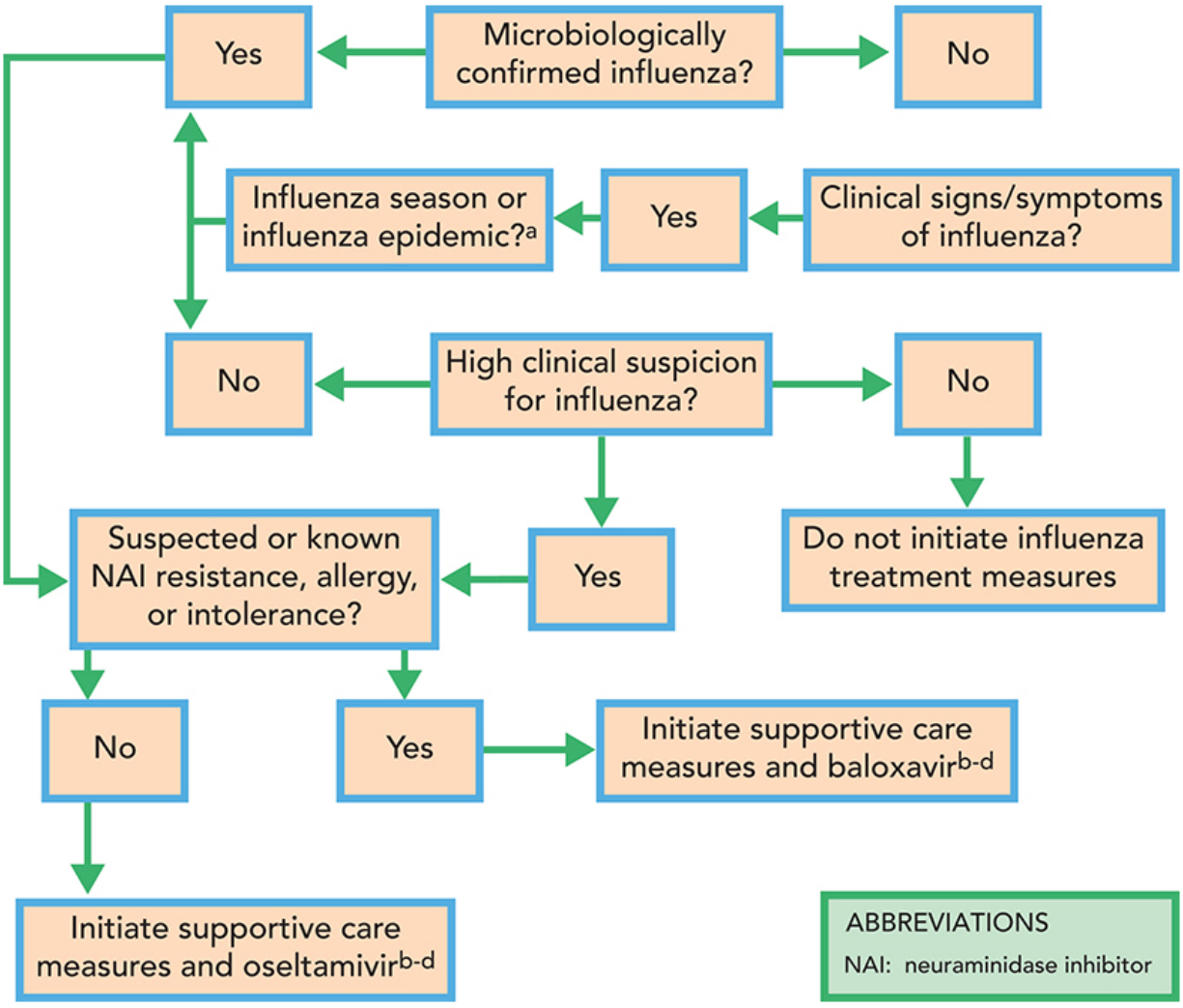
[d]Every 24-h administration recommended in severe/complicated disease. One-time administration in mild/uncomplicated disease.

[e]Cap-dependent endonuclease inhibition.

An approach to the treatment of influenza in the ICU setting is presented in Algorithm 46.1. Of note, the routine use of corticosteroids is not included due to the lack of high-quality data supporting their use. In light of mixed observational evidence associating corticosteroid use with worse clinical outcomes, resistance development, and superinfection, critical care providers must carefully weigh the risks and benefits of corticosteroid administration in the context of other compelling indications or complications. Similarly, the use of other adjunctive therapies, including macrolide antibiotics, cyclooxygenase-2 inhibitors, mammalian target of rapamycin (mTOR) inhibitors, statins, vitamin C, and immune-related therapies (eg, intravenous immunoglobulin

formulations and nitazoxanide), is neither discussed nor supported by current evidence.

ALGORITHM 46.1 **Management of Influenza in Patients Who Are Critically Ill**



[a]A lower threshold to implicate influenza during periods of seasonal influenza/epidemics should be considered.

[b]Treatment within the first 48 h is recommended.

[c]In patients with concerns for enteral absorption of oseltamivir, intravenous peramivir may be considered as an alternative NAI.

[d]Patients with severe illness or highly immunosuppressed may be considered for use of combination therapy with baloxavir, high-dose oseltamivir, and/or extended

treatment duration (eg, >5 d).

Management of Severe Acute Respiratory Syndrome Coronavirus 2

The SARS-CoV-2 or coronavirus-19 (COVID-19) pandemic is responsible for over 1 million total deaths in the United States alone. While case, death, and hospitalization trends have decreased since the peak of the pandemic, the continued evolution and mutation of SARS-CoV-2, combined with its propensity to cause severe disease in elderly patients or those with chronic medical and/or immunocompromising conditions, remain paramount considerations for ICU providers. Like other viral pneumonias, the medical management of COVID-19 begins with appropriate preventive and supportive measures.

To date, several therapeutic agents have been studied for the treatment of COVID-19. In light of rapidly evolving data and evidence, readers are highly encouraged to review appropriate and updated treatment guidelines for COVID-19 management. Table 46.3 and Algorithm 46.2 provide a broad review of available therapeutic agents and the management of patients with severe COVID-19 pneumonia. Like influenza, antiviral therapies (eg, remdesivir) are likely to be most effective early in the course of the disease. At the time of this writing, data are insufficient to recommend routine use of SARS-CoV-2–specific monoclonal antibodies in hospitalized patients for COVID-19. Patients who are critically ill may be considered for treatment directed at the dysregulated immune and inflammatory response associated with COVID-19. Current guidelines stratify the treatment of COVID-19 based on disease severity/oxygen requirements.

TABLE 46.3 **Select Antivirals/Immunomodulators Targeting COVID-19**

Medication	Class/Mechanism	Typical Dosing and Administration	Adverse Effects/Monitoring
Dexamethasone	Corticosteroid	6 mg IV/PO/PT QD[a]	↑ BG, ↑ WBC
Remdesivir	RNA polymerase inhibitor	200 mg IV once, then 100 mg IV QD[b]	↓ HR, ↑ AST/ALT, ↑ SCr
Baricitinib	JAK1 and JAK2 inhibitor	1-4 mg PO/PT QD[c,d]	Infections, ↓ ANC, ↓ Plt, ↑ AST/ALT, GI perforation, drug interactions
Tofacitinib	JAK1 and JAK3 inhibitor[e]	5-10 mg PO/PT BID[c,d]	
Tocilizumab	IL-6 inhibitor	8 mg/kg IV once (max 800 mg)	Infections, ↓ ANC, ↓ Plt, ↑ AST/ALT, GI perforation
Sarilumab	IL-6 inhibitor	200-400 mg IV once	

ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BG, blood glucose; BID, twice a day; GI, gastrointestinal; HR, heart rate; IL, interleukin; IV, intravenous; JAK, Janus kinases; Plt, platelet; PO, by mouth; PT, per tube; SCr, serum creatinine; QD, once daily.

[a]Typical treatment duration is up to 10 d or until hospital discharge.

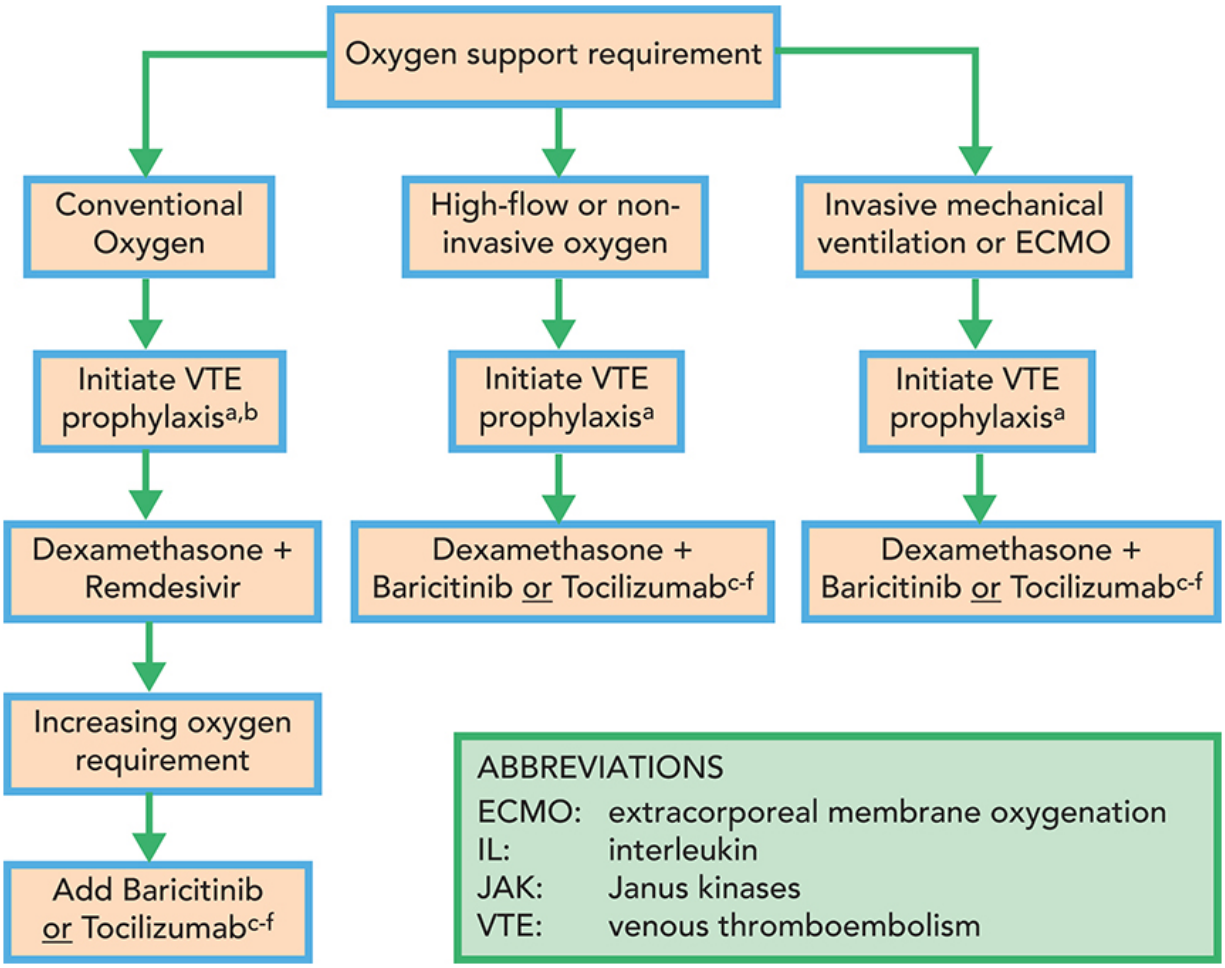
[b]Typical treatment duration is 5 d or until hospital discharge.

[c]Renal dose adjustments required.

[d]Typical treatment duration is up to 14 d or until hospital discharge.

[e]Modest activity against JAK2 described.

ALGORITHM 46.2 Management of COVID-19 in Patients Who Are Critically Ill



[a]If indication for therapeutic anticoagulation is known or identified, initiate therapeutic anticoagulation. If contraindication to VTE prophylaxis exists, it should not be initiated.

[b]Patients with elevated D-dimer levels and low risk of bleed may be considered for therapeutic anticoagulation without known or identified indication on a case-by-case basis.

[c]No high-quality data exist comparing immunomodulator regimens.

[d]Patients with other active infection(s), immunosuppressed, or with liver dysfunction were excluded from clinical trials. Cautious use, if any, of IL/JAK inhibitors is recommended in these populations, and remdesivir may be considered as an alternative option.

[e]Remdesivir may be continued if initiated prior and may be considered in the immunocompromised, those with evidence of ongoing viral replication, or within 10 days of symptom onset.

[f]Tofacitinib and sarilumab, respectively, are alternatives if baricitinib and tocilizumab are unavailable.

In patients who are critically ill presenting with COVID-19, corticosteroids (eg, dexamethasone) remain the cornerstone of management as multiple randomized trials have indicated their ability to improve clinical outcomes and reduce mortality in hospitalized patients requiring any form of supplemental oxygen. Furthermore, rates of secondary infections or other serious adverse events with routine corticosteroid use have not been consistently reported. The addition of remdesivir in hospitalized patients receiving supplemental oxygen, particularly via conventional or high-flow nasal cannula, should be considered, because the combination of remdesivir and dexamethasone was common in studies showing improved outcomes. In patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation support, remdesivir may provide limited or no clinical benefit, but may be considered in the immunocompromised or patients with evidence of ongoing viral replication or within 10 days of symptom onset. Providers must weigh the risks and benefits of continuing or initiating remdesivir in this population. Provided the presence of sulfobutylether beta-cyclodextrin (SBECD) sodium in formulations of remdesivir, cautious use in patients with renal dysfunction is recommended. However, results of post hoc and observational analyses suggest that the use of remdesivir in this population is safe if the perceived benefit outweighs the risk. Other immunomodulating agents, such as interleukin inhibitors (eg, tocilizumab, sarilumab) or Janus kinase inhibitors (eg, baricitinib, tofacitinib), must be considered on a case-by-case basis, considering the efficacy and safety profile of each agent. Randomized trials investigating their use have included patients receiving noninvasive and invasive mechanical ventilation and/or those with elevated inflammatory markers (eg, ferritin, C-reactive protein); however, various populations have been underrepresented in these studies (eg, immunosuppressed, active other infection). While data are mixed, improved outcomes with the addition of a second immunomodulator to dexamethasone have been seen in clinical trials. Furthermore, an absence of significant safety findings in available evidence should further solidify the routine consideration and use of additional

immunomodulators in patients requiring ICU level care. To date, high-quality, comparative trials between immunomodulators have not been performed. Providers may prefer the use of tocilizumab or baricitinib, given the more robust evidence and experience with these agents in ICU patients. Readers are referenced to Table 46.3 and Algorithm 46.2 for important considerations surrounding appropriate agent selection and dosing.

Venous thromboembolism (VTE) is a well-described complication of COVID-19. The empiric use of therapeutic anticoagulation in patients who are critically ill receiving high-flow, noninvasive, or invasive mechanical ventilation without a known VTE or alternative indication is not recommended. Available data suggest a lack of improvement in hard outcomes compared to the use of venous thromboembolism prophylaxis. Notably, randomized data have shown significant improvements in various outcomes for patients requiring conventional oxygen therapy who received therapeutic anticoagulation compared to prophylaxis for VTE. However, routine use of therapeutic anticoagulation in ICU patients requiring conventional oxygen must be carefully weighed against the potential for an increased risk of bleeding.

SUGGESTED READINGS

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SECTION XI RENAL DISORDERS

47 Acute Kidney Injury

Jason Cummings and Anitha Vijayan

Acute kidney injury (AKI), previously known as acute renal failure, is manifested by a rapid decline in renal function, usually with decreased urine output and the accumulation of end products of nitrogen metabolism. It is a common clinical problem encountered in patients who are critically ill, frequently in the setting of multiple organ failure, and is an independent risk factor for increased in-hospital and long-term mortality. In one multicenter study, the incidence of AKI in the intensive care unit (ICU) was found to be 57%, with sepsis being attributed as the etiology in 41% of cases.

Definition

The lack of a consensus definition for AKI confounds comparisons between studies of prevention, therapy, and outcomes. The RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria and the Acute Kidney Injury Network (AKIN) criteria have now been replaced by the Kidney Disease: Improving Global Outcomes (KDIGO) staging of AKI (Table 47.1), which provides a single definition for clinical practice, research, and public health purposes.

TABLE 47.1 KDIGO Staging of AKI

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6-12 h

Stage	Serum Creatinine	Urine Output
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL OR Initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h OR Anuria for ≥12 h

Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.
AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

The KDIGO clinical practice guidelines for AKI included a revised definition of AKI while retaining the AKIN staging criteria. The timeframe for an increase in serum creatinine of 0.3 mg/dL or more is retained, while the timeframe for a 1.5 times increase or more in serum creatinine is changed to 7 days.

Patients with AKI are frequently classified as being nonoliguric (urine output >400 mL/d), oliguric (urine output <400 mL/d), or anuric (urine output <100 mL/d). Lower urine output suggests more severe renal injury and is associated with poorer outcomes. Prognosis is also worse in patients who require renal replacement therapy. Therefore, timely diagnosis is crucial as identifying and promptly treating the cause of renal injury may hasten recovery and prevent the need for dialysis.

Diagnostic Approach to the Patient With Acute Kidney Injury

AKI is a syndrome of multiple etiologies. An algorithmic approach in the evaluation of AKI is mandatory. In many cases, gathering patient's history, conducting a thorough physical examination, and analyzing laboratory data including urinalysis, urine electrolytes, and urine sediment examination along with radiography and review of

medications and diligent attention to available medical records, will provide the necessary information in making such a determination. Special attention should be given to the 24 to 48 hours prior to the rise in serum creatinine, as it may serve as a lagging indicator of renal injury.

Urine Chemistries

URINE SODIUM

A spot urine sodium measurement can be used to determine the salt avidity of the tubules, with a low urine sodium, less than 20 mmol/L, reflecting salt avid tubules. This can be seen in patients with decreased renal perfusion secondary to either absolute volume depletion or decreased effective arterial volume. A low urine sodium reflects the kidney striving to reclaim salt and water to restore intravascular volume. In contrary, a high urine sodium, more than 40 mmol/L, is indicative of salt wasting. This can be seen in acute tubular necrosis (ATN), as the necrosed tubule cells are unable to reabsorb sodium. Please note that patients with decreased urinary concentrating ability, such as old individuals or those with chronic kidney disease (CKD), may not be able to generate such a low urinary sodium. It is important to appreciate that the fractional excretion of sodium, or FENa, which has historically been used to inform differential diagnoses of kidney injury can be confounded by a plethora of renal conditions, including acute glomerulonephritis, contrast nephropathy, pigment-induced ATN, transplant rejection, and early urinary obstruction. FENa has not proven to be useful in establishing a diagnosis or prognosis in patients who are critically ill and should be interpreted with caution in the ICU.

URINALYSIS AND URINE MICROSCOPY

The urinalysis and urine microscopy provide valuable clues to underlying etiology of AKI. On urinalysis, the presence of nitrites and

leukocyte esterase is suggestive of infection, the presence of blood without visualized red blood cells is suggestive of myoglobinuria, and the presence of blood and protein is suggestive of a potential glomerular process. Examination of the urinary sediment by a nephrologist is essential as abnormal urinary sediment is strongly suggestive of an intrarenal process. “Muddy” granular casts and renal tubular epithelial cell (RTEC) casts are most often seen in ATN. Red blood cell casts and dysmorphic red blood cells suggest a glomerular origin, and white blood cell casts are found when inflammation is present in the interstitium as in acute interstitial nephritis (AIN) and pyelonephritis. It is important to note that red and white blood cell casts are fragile and that their absence alone does not necessarily eliminate their associated disorders from the differential diagnosis. Bland sediment and hyaline casts are consistent with prerenal AKI. Since it is believed that prerenal AKI and ATN are a spectrum and may coexist, it would be helpful to assess the urine findings quantitatively (numbers of cells or casts per low- or high-power field). Different scoring systems have been developed, showing a correlation between an increased number of RTECs or granular casts and poor renal recovery. Urine microscopy, performed by a trained physician, holds significant diagnostic and prognostic value in patients who are critically ill and should be strongly encouraged.

URINE BIOMARKERS

Several urine biomarkers are approved for clinical use for prediction of AKI. These include neutrophil gelatinase–associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), tissue inhibitor of metalloprotease 2 (TIMP-2), and insulin-like growth factor–binding protein 7 (IGFBP7). In 2014, the U.S. Food and Drug Administration (FDA) approved the marketing of (TIMP-2) × (IGFBP7) under the brand name NephroCheck as the first and only biomarker for AKI risk stratification in the United States. It is indicated for use in ICU patients aged 21 years and older with cardiovascular and/or respiratory compromise within the prior 24

hours. NephroCheck aids in the risk assessment for moderate or severe AKI. A positive test result (value >0.3) indicates a high risk for AKI within 12 hours, prompting consideration for nephrology consultation and implementation of preventive strategies like optimizing volume status and avoiding nephrotoxic drugs.

Etiology of Acute Kidney Injury

When determining the etiology of AKI, it can be helpful to divide AKI into subtypes, including prerenal, intrinsic, and postrenal etiologies. Intrinsic kidney injury can be further subdivided into tubular, glomerular, vascular, and interstitial etiologies.

PRERENAL ACUTE KIDNEY INJURY

Etiology

In the prerenal process, the integrity of renal parenchyma is preserved. The decreased glomerular filtration rate is a physiologic response to renal hypoperfusion that is due to either true or effective volume depletion. Examples of true volume depletion include hemorrhage and gastrointestinal losses, whereas decreased effective volume is seen in decompensated heart and liver failure, nephrotic syndrome, and anaphylaxis. Renal vasoconstriction can be caused by hypercalcemia and calcineurin inhibitors, and impairment of renal autoregulation by nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are common scenarios leading to prerenal azotemia. Hypoperfusion may also result from sustained intra-abdominal pressure more than 20 mm Hg, measured by transducing a pressure via indwelling Foley catheter, leading to abdominal compartment syndrome. This syndrome can be seen in intra-abdominal hemorrhage, massive ascites, severe pancreatitis, bowel distension, and major abdominal surgery including postliver transplantation.

Diagnosis

The diagnosis is suspected based on the patient's history and physical examination. For example, the patient may endorse a 3-day history of nausea, vomiting, diarrhea, and poor oral intake. Vital signs in such a scenario may reveal tachycardia and hypotension. On physical examination, findings may include dry mucous membranes, decreased skin turgor, and prolonged capillary refill time. Urine chemistry reflects the appropriate tubular response to hypoperfusion, with avid sodium reabsorption. The urine sodium is usually less than 20 mmol/L. The urine is markedly concentrated and urine osmolality is usually more than 500 mOsm/kg. In prerenal AKI, the urine sediment is typically bland, lacking cells, crystals, and cellular casts.

Management

Rapidly addressing the cause of renal hypoperfusion is crucial, as prolonged ischemia can lead to renal tubular injury and eventual necrosis. All offending drugs/agents should be discontinued immediately.

In cases of hypovolemia, intravascular depletion must be reversed. However, the choice of type, volume, and infusion rate of intravenous fluids in patients who are critically ill remain controversial. With regard to crystalloid solutions, balanced solutions offer no significant clinical advantage over 0.9% sodium chloride, based on two large multicenter randomized controlled trials—BASICS and PLUS trials. Balanced solutions should be avoided in patients with traumatic brain injury. Lactated Ringer solution has been suggested for its anti-inflammatory effect in patients with acute pancreatitis. Additionally, balanced solutions are safe and effective in patients with hyperkalemia, given their low potassium concentration (4 mEq), particularly given that the acidity of 0.9% sodium chloride (pH 5.4) can perpetuate a hyperchloremic nonanion gap acidosis which may result in extracellular shifting of potassium, and ultimately worsening hyperkalemia. Regarding colloids, the SAFE trial revealed no difference in 4% albumin compared to 0.9% sodium chloride for

fluid resuscitation. Albumin should be avoided in head injuries. The evidence-based indications for albumin remain sparse and include second-line therapy for septic shock (with a potential benefit when combined with crystalloids), diagnosing hepatorenal syndrome, treating spontaneous bacterial peritonitis, and resuscitation following large-volume paracentesis. Starch-containing solutions are associated with increased mortality and should be avoided. If the patient's prerenal state is secondary to hemorrhage, blood products should be administered in a balanced manner or, alternatively, with whole blood.

In conditions associated with decreased effective arterial volume, such as decompensated heart or liver failure, treatment should focus on maintaining renal perfusion and achieving euvolemia.

Managing volume overload in the setting of acute decompensated heart failure can be particularly challenging. The pathophysiology driving AKI in type 1 cardiorenal syndrome, or an acute alteration in renal function when congestive heart failure is present (the most frequently encountered type of cardiorenal syndrome seen in the ICU setting), centers on renal venous congestion compromising glomerular filtration rate (GFR). As such, treatment should be targeting decongestion. This requires consideration of numerous factors, including premorbid renal function, electrolyte abnormalities, and acid-base status. When decongestion goals are not met, close attention must be given to type, dose, route, and frequency of diuretic. Moreover, diuretics of different classes may be combined in concert to achieve sequential nephron blockade. A spot urine sodium can be obtained 1 to 2 hours after administration of diuretics to assess diuretic response. A value of less than 50 mmol/L is generally insufficient to induce a negative sodium balance. It should be noted that a stepped pharmacologic-therapy algorithm has been demonstrated to be superior to a strategy of ultrafiltration as both methods achieved a similar amount of weight loss, with ultrafiltration being associated with a higher rate of adverse events. Positive inotropes, afterload reduction, and even mechanical circulatory support devices may also be used. Invasive and dynamic hemodynamic monitoring can guide management when intravascular

volume status is difficult to determine based on traditional physical examination findings.

Management of hepatorenal syndrome (HRS) is a serious but potentially reversible complication of end-stage liver disease as well as fulminant hepatic failure of any cause (eg, tumor infiltration and acetaminophen toxicity). It is a result of severe intrarenal vasoconstriction in the setting of splanchnic vasodilatation and effective hypovolemia. It can occur spontaneously in advanced liver disease or develop after a precipitating event such as infection (eg, spontaneous bacterial peritonitis), gastrointestinal bleeding, or large-volume paracentesis without supplemental albumin. In patients with spontaneous bacterial peritonitis, albumin infusion may prevent development of HRS.

HRS is a diagnosis of exclusion (see Table 47.2, for diagnostic criteria of HRS). The prognosis of HRS-AKI (formerly HRS-type 1) is very poor as there are limited therapeutic strategies in HRS. These include increasing intravascular volume with albumin, increasing mean arterial pressure (MAP) by 10 mm Hg with either oral or intravenous vasopressors (midodrine and epinephrine, respectively), and decreasing splanchnic vasodilation with a somatostatin analog (octreotide). Terlipressin, a synthetic vasopressin analog with splanchnic vasoconstrictor activity has demonstrated improvement in renal function in patients with HRS and AKI and was approved for use in the United States in 2022. Respiratory failure is a possible complication of terlipressin, particularly in patients with volume overload, and oxygenation status must be monitored closely. Liver transplantation is the only definitive treatment. Resolution of HRS can occur with improvement in hepatic function in the cases of acute liver injury and alcoholic hepatitis. Renal replacement therapy should primarily be reserved for those whose liver function is expected to recover or those who are candidates for liver transplantation.

TABLE 47.2 Diagnostic Criteria of Hepatorenal Syndrome

- Cirrhosis with presence of ascites

- Worsening renal function over days to weeks with serum creatinine at least 1.5 mg/dL
- Absence of intrinsic renal disease as indicated by proteinuria (>500 mg/d), microscopic hematuria (>50 red blood cells per high-power field), and/or structural abnormalities detected by imaging studies.
- Absence of shock
- Absence of concurrent or recent use of nephrotoxic medications
- No improvement of renal function after diuretic withdrawal and volume expansion with albumin for at least 2 d. Albumin should be dosed 1 g/kg of body weight per day up to a maximum of 100 g/d.

SUBTYPES

Type 1: Rapidly progressive form, with doubling of serum creatinine to a level >2.5 mg/dL in <2 wk

Type 2: Moderate renal failure, with a slowly progressive course. Serum creatinine 1.5-2.5 mg/dL. Typically associated with refractory ascites

From Salerno F, Gerbes A, Ginès P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56(9):1310-1318, with permission from *BMJ* Publishing Group Ltd.

Postrenal Acute Kidney Injury

A postrenal process occurs when the GFR is decreased secondarily by an impediment to urine outflow because of structural or functional changes in the urinary tract. This is a very rare cause of AKI in the ICU. The increased pressure in the urinary tract is conveyed proximally from the obstruction, resulting in a rise in tubular pressure and an eventual decrease in the hydraulic pressure gradient across the glomerular capillaries, leading to a decline in GFR as well as changes in tubular function. This may manifest as decreased concentrating ability or distal renal tubular acidosis.

Urinary obstruction can be unilateral or bilateral, acute or chronic, partial or complete, and intrarenal (tubular obstruction from crystals, casts) or extrarenal. Clinical symptoms vary according to the duration, degree, and site of obstruction. Unilateral obstruction does

not typically lead to renal failure. Urine output is nondiagnostic, except in the case of anuria that suggests complete obstruction.

The diagnosis is initially suspected based on the history and physical examination and is confirmed by findings of hydronephrosis on renal ultrasound or computed tomography (CT). Absence of hydronephrosis on radiologic testing does not completely exclude obstruction. In the setting of severe volume depletion, retroperitoneal fibrosis, and in the very early phase of obstruction, dilatation of the calyces may not occur and ultrasound may be falsely negative. A simple method to evaluate for distal obstruction is measurement of the postvoid residual, a residual more than 100 mL is consistent with bladder outlet obstruction. Obstruction of the Foley catheter with clots should also be considered; this is ruled out either by flushing the catheter or by replacing it entirely. In the intensive care setting, unless there is high index of suspicion based on the clinical picture (eg, recent abdominal surgery, history of malignancy, and anticholinergic medications), the yield from renal ultrasound is low.

Once the diagnosis of urinary obstruction/obstructive nephropathy is made, prompt intervention is necessary to minimize long-term renal impairment as marked loss of renal parenchyma can be seen in just 1 to 2 weeks. The method of intervention is dictated by the location and cause of the obstruction. Postobstructive diuresis with marked polyuria is often seen after relief of complete obstruction. Although this is considered an appropriate response in many cases, volume depletion and electrolyte imbalances can occur and require close monitoring and intervention.

Intrinsic Acute Kidney Injury

Intrinsic renal disease is present when the injury is at the level of the kidney parenchyma. Further classification depends on the area of involvement: glomeruli, vasculature, tubules, or interstitium. Such differentiation can frequently be achieved by careful analysis of the urine sediment, as mentioned before. In the critical care setting, ischemic and nephrotoxic ATN account for up to 90% of intrinsic AKI.

ACUTE TUBULAR NECROSIS

Etiology

ATN can result from ischemia due to prolonged prerenal states or toxins, be it endogenous, such as myoglobin, or exogenous, such as amnioglycosides or certain cancer treatments. In severe cases, renal hypoperfusion can result in bilateral cortical necrosis, which may lead to prolonged need for renal replacement therapy and sometimes irreversible renal damage.

Diagnosis

In the critical care setting, nephrotoxic insults are usually simultaneous or sequential, and no single precipitating factor can be identified. As previously stated, history and comprehensive chart review are of the utmost importance. For example, bariatric surgery or extensive downtime following an unintentional overdose time may lead to skeletal muscle break down, toxic myoglobin release, and rhabdomyolysis. With severe, repeated or prolonged injury, the renal tubules lose their ability to retain sodium and concentrate urine. Examination of the urine sediment can reveal RTECs and muddy brown granular casts in a majority of the patients. Because the glomeruli and interstitium are typically spared, other urinary findings such as heavy proteinuria and hematuria are absent.

Management

There is no specific treatment of ATN once it has occurred. Therapy is generally supportive and includes the use of renal replacement therapy if necessary. Attempts to reverse the initial insult should be made. Management should also focus on avoiding additional nephrotoxic insults, adjusting drug doses appropriately for the level of renal function, and ensuring adequate renal perfusion. Depending on the cause and severity, as well as the baseline renal function, renal recovery takes days, weeks, or even months, if at all. Generally, renal recovery can be expected in about 75% of patients

who previously had normal baseline function, provided they survive the hospitalization.

GLOMERULAR AND MICROVASCULAR PROCESSES

Glomerular causes of renal injury are much less common in an acute intensive care setting (Table 47.3). The vasculitides should be suspected in patients with constitutional symptoms in addition to kidney injury and an active urinary sediment. The pulmonary-renal syndromes of granulomatosis with polyangiitis (GPA) and Goodpasture disease should be considered in anyone presenting with simultaneous respiratory and renal dysfunction, as they are universally fatal if not recognized and treated in a timely manner. Serologic tests are helpful in these cases. The presence of red blood cell casts specifically suggests a glomerular origin. A kidney biopsy may ultimately be necessary for a definitive diagnosis in patients with intrinsic pathology.

TABLE 47.3 Selected Glomerular and Microvascular Disorders in the Intensive Care Unit

Cause	Characteristics	Treatment
Immune complex	Hypocomplementemia seen with postinfectious GN, MPGN, SLE, endocarditis, and cryoglobulinemia	Treat the underlying cause

Cause	Characteristics	Treatment
Pauci-immune and anti-GBM disease	Pulmonary hemorrhage syndromes may have positive serum c-ANCA or p-ANCA or anti-GBM antibody (Goodpasture) Dysmorphic RBCs in urine suggest glomerular origin	Supportive therapy for pulmonary compromise, mechanical ventilation if necessary Corticosteroids and cytotoxic agents Plasma exchange for Goodpasture or vasculitis with pulmonary hemorrhage or advanced renal failure
Microvascular	HUS and TTP with low platelets, hemolytic anemia, and schistocytes on peripheral smear Atheroembolic disease Subacute renal failure, days to weeks after invasive vascular procedure, with livedo reticularis and transient peripheral eosinophilia	TTP requires emergent plasma exchange Supportive care for HUS Refractory TTP may benefit from immunosuppression with prednisone and/or rituximab Avoid anticoagulation and further vascular procedures

c-ANCA, cytoplasmic antineutrophilic cytoplasmic antibody; GBM, glomerular basement membrane; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; MPGN, membranoproliferative glomerulonephritis; p-ANCA, perinuclear antineutrophilic cytoplasmic antibody; RBCs, red blood cells; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

The antiglomerular basement membrane antibody is a highly sensitive (95%) and specific test (99%) for Goodpasture disease. In GPA, the serine proteinase 3 antibody (c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody) is elevated in more than 75% of cases; approximately 20% have an elevated myeloperoxidase antibody (p-ANCA) and less than 5% are ANCA-negative. Treatment of these syndromes is with immediate intravenous corticosteroids (methylprednisolone at 7-15 mg/kg/d and/or up to 1 g/d for 3 days followed by oral prednisone at 1 mg/kg/d up to 60-80 mg) and with

cytotoxic immunosuppressants (oral cyclophosphamide at 2-3 mg/kg/d, intravenous cyclophosphamide at 15 mg/kg or 750 mg/m^2). Therapeutic plasma exchange is also employed in the treatment of Goodpasture disease. In ANCA-positive vasculitis with advanced renal failure, one study demonstrated that the single predictive factor associated with long-term independence from dialysis was the use of therapeutic plasma exchange. Therapeutic plasma exchange is also recommended for the management of pulmonary hemorrhage associated with ANCA-positive vasculitis. The differential diagnoses of pulmonary-renal syndromes include community-acquired pneumonia with sepsis and ATN, systemic lupus erythematosus with lung involvement and lupus nephritis, sarcoidosis, and infections such as leptospirosis, legionella, ehrlichiosis (pneumonia with AIN or ATN), and pancreatitis with pneumonia and ATN.

Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two distinct thrombotic microangiopathies that can result in renal injury. These patients classically present with difficult-to-control hypertension, anemia, thrombocytopenia, and renal dysfunction. In addition to presenting similarly, they share several common precipitating factors such as human immunodeficiency virus (HIV) infection, malignancy, calcineurin inhibitors, pregnancy, and chemotherapeutic agents. Ticlopidine and, less commonly, clopidogrel are more closely associated with TTP. If TTP is suspected, an ADAMTS13 level should be obtained. In the diarrheal form of HUS, a Shiga-like toxin enters the circulation through compromised colonic epithelium and results in inflammation, endothelial injury, and thrombosis in the renal microvasculature. Therapy is supportive for Shiga toxin–associated HUS, with no proven efficacy of antibiotics, anticoagulation, immunoglobulin, or plasmapheresis. However, in atypical HUS (aHUS), humanized monoclonal antibody inhibiting the action of complement factor C5 (eculizumab) has been shown to be beneficial. Additionally, these patients should undergo genetic testing for mutations in the alternative complement pathway. In the case of TTP, daily plasma volume exchange is a life-saving therapy and thus must not be delayed. In resistant cases, immunosuppression with

high-dose prednisone and rituximab can be used. Splenectomy has been attempted in refractory cases, but is of unproven benefit.

Lastly, atheroembolic disease is a microvascular disease that can be diagnosed in patients who are critically ill who have undergone endovascular procedures, should there be a high index of suspicion. Transient peripheral eosinophilia may be present in more than 65% of cases. Hypocomplementemia can be seen in the initial phase of the disease. Skin findings are highly variable and may include livedo reticularis of the extremities or digital necrosis with gangrene (blue toe syndrome). Distal pulses are typically present as the occlusion is at the level of smaller arteries and arterioles. The general rule from the renal standpoint is a slow decline in renal function during months, with a third of the patients requiring dialysis. In multivisceral atheroembolic disease, manifested by intestinal ischemia, pancreatitis, and other systemic manifestations, 1-year mortality can be as high as 70%. There is no effective medical treatment. Avoidance of further vascular procedures along with judicious control of blood pressure, use of angiotensin-converting enzyme inhibitors (ACEIs), and nutritional support have also been associated with better prognosis. A case series has noted a possible benefit from statin therapy in improving the long-term renal outcome.

INTERSTITIAL PROCESSES

AIN is an inflammatory process caused by medications or by infections. Beta-lactam antibiotics are common culprits, although nearly every antibiotic and many nonantibiotic medications have been implicated. The classic triad of rash, eosinophilia, and fever is not commonly seen. Urinary findings suggestive of AIN include white blood cells, white blood cell casts, and eosinophils. Occasionally, the urine sediment can be bland. Eosinophiluria is a nonspecific finding and has a relatively low sensitivity and specificity and add little value in diagnosing AIN. Renal biopsy may be necessary to establish a definitive diagnosis.

Removal of the offending agent or treatment of the underlying infectious disease is the mainstay of therapy. Recovery of renal

function may not occur for days to weeks, and sometimes several months. The role of corticosteroid therapy remains controversial. Some studies suggest a better outcome in patients who are treated with steroids. Cyclophosphamide, mycophenolate mofetil, or other immunosuppressants have also been used in corticosteroid nonresponders after 2 to 3 weeks of therapy.

Summary

An algorithmic approach to AKI is paramount for uncovering its etiology and devising a treatment plan. Adroit history-taking, thorough physical examination, and a comprehensive review of medications are of unparalleled importance. The history and physical examination findings should be substantiated with laboratory data and imaging studies. Microscopic examination of the urine sediment is highly valuable in identifying the underlying renal disorder and may help in further classifying some disorders. Considering etiologies as prerenal, intrinsic, or postrenal in nature will greatly aid in narrowing the differential diagnosis. In cases of glomerular injury and interstitial nephritis, immunosuppression may be required to reverse the disease process. However, the majority of AKI cases in the ICU is due to tubular injury (ATN), and specific therapies are not available for reversing or preventing further progression of the injury. Treatment remains supportive, primarily with renal replacement therapy, which will be discussed in the next chapter (Chapter 48, Renal Replacement Therapy).

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48 Renal Replacement Therapy

Jason Cummings and Anitha Vijayan

The principal strategy regarding acute kidney injury (AKI), particularly in the intensive care setting, is prevention. Once AKI occurs, the presentation and course are variable and treatment is generally supportive. Certain patients with AKI will require renal replacement therapy (RRT) while in the intensive care unit (ICU) and, perhaps, beyond.

Indications

Conventional indications for RRT include metabolic acidosis, hyperkalemia, volume overload, and severe uremic symptoms refractory to medical management. Other indications include certain intoxications of certain substances (ethylene glycol, methanol, lithium, etc), where either the substance or the toxic metabolite will be cleared with dialysis. Patients with chronic kidney disease (CKD) stage 3 or higher have a substantial increase in risk of developing AKI requiring dialysis.

ACIDOSIS

Refractory metabolic acidosis is an acute indication for dialytic therapy in the severely ill patients. Progressive acidemia can develop as the kidneys lose their ability to reclaim bicarbonate and excrete organic acids. More commonly in the intensive care setting, tissue hypoperfusion with multiorgan system failure results in severe lactic acidosis. Aggressive alkali therapy can cause problems with volume overload, metabolic alkalosis, and hypocalcemia. Initiation of

RRT would obviate the concern over volume overload and could restore the blood pH to its physiologic range.

HYPERKALEMIA

Hyperkalemia can be rapidly fatal and needs to be addressed promptly. An electrocardiogram (ECG) revealing peaked T waves can be a specific but not sensitive manifestation of life-threatening hyperkalemia. Temporizing measures include intravenous calcium to stabilize the myocardial cell membrane, as well as insulin (with dextrose 50% in water), sodium bicarbonate, and inhaled beta-agonists (at a 3-4 times higher dose than for bronchodilation) to promote an intracellular shift in potassium. Elimination of potassium from the body can be achieved with ion-exchange resins. In the volume-depleted patient, aggressive fluid resuscitation can enhance sodium delivery to the distal nephron. The reabsorption of sodium makes the lumen electronegative, promoting secretion of potassium via the potassium channel, and, ultimately, kaliuresis.

When these efforts are unsuccessful, urgent RRT becomes necessary. Intermittent hemodialysis (IHD) with higher blood flow and dialysate flow rates is very effective in lowering potassium rapidly and is the preferred modality of choice. The patients are dialyzed using a 0 or 1 mEq/L potassium concentration in the dialysate. However, in a critically ill patient with hypotension with or without pressors, continuous renal replacement therapy (CRRT) with high-flow rates (>35 mL/kg/h) of replacement fluid and dialysate with 0 potassium concentration can also be utilized to lower potassium levels.

VOLUME OVERLOAD

Volume overload is another frequently encountered problem in the critical care setting. There is evidence that in patients with AKI, fluid overload is an independent risk factor for mortality. Although randomized trials studying the use of diuretics in AKI have not demonstrated any survival advantage, improvement in renal

recovery, or avoidance of dialytic therapy, it is not unreasonable to offer a trial of intravenous high-dose loop diuretic (eg, 160-200 mg of furosemide or 4-5 mg of bumetanide) in the setting of fluid overload. Sequential nephron blockade should also be utilized, which involves simultaneous administration of diuretics with differing mechanisms of action, that is, thiazide and loop diuretics, to maximize diuresis. Respiratory compromise with pulmonary edema and significant soft tissue edema that impairs the barrier defense of the skin is the most common subjective criteria for initiating renal replacement in the patient with oliguria.

UREMIA

With progressive renal dysfunction, there is an impaired ability to excrete nitrogenous wastes and glycosylated end products. Blood urea nitrogen (BUN) level is generally used as a surrogate marker for uremic toxin accumulation. Unfortunately, many signs and symptoms commonly found in the uremic syndrome do not always correlate with BUN levels, and therefore there is no established objective cutoff beyond which dialytic therapy is recommended. Rather, acute indications for initiating urgent RRT center on the presence of specific clinical findings, namely uremic encephalopathy and uremic pericarditis. The latter possesses a high risk of converting into hemorrhagic pericarditis with cardiac tamponade. Systemic anticoagulation should be avoided in such patients.

Timing of Initiation of Renal Replacement Therapy

Since 2016, five large clinical trials have addressed the timing of initiation of RRT in critically ill patients with AKI and have given us valuable information regarding this important decision. Early and smaller studies suggested a survival advantage with early initiation (definition varies greatly among studies; most used BUN <60 vs >60). Subsequent randomized control studies in populations more

reflective of those in medical ICUs evaluating the timing of initiation of RRT on outcomes have not shown a benefit with early initiation of RRT. The sum of these trials favors initiation of RRT when a specific complication of AKI occurs (eg, severe hyperkalemia) rather than starting based on the stage of AKI or simply a rise in serum creatinine. However, waiting too long, that is, BUN greater than 140, may not be in the best interest of the patient. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend initiating RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. The Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial standard arm criteria consisting of the following parameters are considered acceptable indications for initiation of RRT for AKI in the critical population.

- Persistent AKI, with Cr more than 50% of the value recorded at randomization along with one of the following features:
  - K^+ more than 6 mmol/L
  - pH less than 7.2 or HCO_3 less than 12 mmol/L
  - Fluid overload causing respiratory compromise (PaO_2/FIO_2 <200)
  - Persistent AKI for more than 72 hours from randomization

Modalities

Once the decision has been made to initiate RRT, one needs to select a modality. The available modalities are IHD, CRRT, prolonged intermittent renal replacement therapy (PIRRT), or peritoneal dialysis. The choice depends on the availability of therapies at the institution, physician preference, the patient's hemodynamic status, and the presence of comorbid conditions. Intermittent modalities generally cause greater fluctuations in blood pressure and produce greater fluid shifts in a short amount of time. Continuous modalities allow for the same solute clearance and fluid

removal, but spread out during a 24-hour period, and thus are favored in patients who is hemodynamically unstable such as those with sepsis or fulminant hepatic failure.

In the United States, CRRT is performed in approximately 30% of adult patients with AKI and has almost completely replaced peritoneal dialysis in the ICU setting. However, although CRRT has some potential benefits over IHD, as seen in randomized trials, CRRT has not shown improved survival over IHD in critically ill patients. Likewise, randomized trials have not shown a difference in time to renal recovery or length of ICU or hospital stay between groups treated with IHD versus CRRT.

In recent years, the use of PIRRT or sustained low-efficiency dialysis (SLED) has increased and is mainly driven by its convenience and lower cost compared to CRRT. Treatments are intermittent but with longer duration (8-12 hours/session), and with lower blood and dialysate flow rates, compared to IHD. Compared to CRRT, PIRRT is performed with higher blood flow and dialysate flow rates. PIRRT is often performed 5 to 6 times per week, usually during the night at some institutions including ours. It is an excellent modality for those patients who are prone to hemodynamic instability. It also provides “downtime” for procedures and physical therapy, while at the same time does not compromise the dialysis dose. PIRRT requires less anticoagulation than CRRT, demands less nursing care, and is a good alternative to CRRT in the ICU. Randomized, controlled studies have suggested similar safety and efficacy compared to CRRT and IHD.

Table 48.1 lists the advantages and disadvantages of the different modalities of dialysis.

TABLE 48.1 Renal Replacement Modalities

Modality	Advantages	Disadvantages

Modality	Advantages	Disadvantages
IHD	High-efficiency transport of solutes when rapid clearance of toxins or electrolytes is required Allows time for off-unit testing	Hemodynamic intolerance secondary to fluid shifts “Saw-tooth” pattern of metabolic control between sessions
CRRT	Gentler hemodynamic shifts than IHD Steady solute control	Continuous need for specialized nursing Requires continuous anticoagulation (heparin vs citrate)
PIRRT	All of the advantages of CRRT Provides “downtime” for off-unit testing Less nursing care than CRRT Less expensive than CRRT Anticoagulation generally not necessary	Requires almost daily treatments Less “middle molecule” removal than CRRT
Peritoneal dialysis	Gentler hemodynamic shifts than IHD	Requires invasion of peritoneal cavity, which may not be possible in postoperative patients Less predictable fluid removal rates

CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; PIRRT, prolonged intermittent renal replacement therapy.

Dialysis Dose

The ideal dose of dialytic therapy in critically ill patients has not yet been conclusively determined. Evidence from patients who are dependent on dialysis at the end-stage of kidney disease suggests that a thrice-weekly regimen should be performed with a urea reduction of approximately 70% per session. However, in the acutely

ill intensive care population, these calculations are not always equivalent. The actual urea clearances are approximately 25% lower than what would be expected in a patient with stable chronic kidney disease requiring dialysis, and thus it has been proposed that additional benefit may be derived from higher treatment doses, more frequent treatments, or greater hemofiltration.

In IHD, a few small studies had shown a survival advantage in critically ill patients who received either a higher delivered dialysis dose 3 times per week or undergo daily dialysis. In contrast, the VA/NIH Acute Renal Failure Trial Network (ATN) study, a large multicenter, prospective, randomized trial, did not find a decrease in mortality or increase in renal recovery with more frequent dialysis (6 times per week vs 3 times). We recommend IHD be provided 3 times a week, targeting the urea reduction ratio of more than 70%, or K_t/V of 1.2 to 1.4 per treatment.

Similarly, in CRRT, small randomized controlled trials had shown a survival benefit with high-intensity dialysis. Subsequent trials have shown conflicting results. The largest trials to date, the ATN study (effluent rate of 35 mL/kg/h vs 20 mL/kg/h) and the study from the RENAL Replacement Therapy Study Investigators (effluent rate of 40 mL/kg/h vs 25 mL/kg/h), did not demonstrate a survival advantage with higher-intensity dialysis at day 60. In the ATN study, higher-intensity dialysis did not improve recovery of renal function or reduce the rate of nonrenal organ failure. Subsequent meta-analyses showed similar results. If continuous venovenous hemodiafiltration (CVVHDF) is the preferred modality at the institution, we recommend using flow rates of 20 mL/kg/h, divided equally between the replacement flow rate and dialysate flow rate. With this dosing, we recommend that patients remain on therapy for a minimum of 20 hours/day. If the patient is not receiving at least 18 to 20 hours of CRRT in a 24-hour period, because of diagnostic testing, surgical procedures, clotting of the circuit, or other factors, then the prescribed dose can be increased by 15% to 20% to ensure that delivered dose will be about 20 mL/kg/h. Also, in patients who need

higher clearances for severe acidosis or hyperkalemia, higher flow rates should be used.

Drug Dosing During Continuous Renal Replacement Therapy

Various factors affect the dosing of medications in the setting of CRRT. The pharmacokinetics of drug removal during CRRT can be highly complex, depending on the drug's molecular size, protein binding, volume of distribution, dialyzer membrane permeability, the dose of dialysis, and the modality of CRRT (continuous venovenous hemodialysis [CVVHD] vs continuous venovenous hemofiltration [CVVH] vs CVVHDF). The clearance of a drug can also be affected by its elimination by nonrenal routes or by the degree of residual renal function. Generally, the nonrenal clearance is taken to be constant, although in critically ill patients with multiorgan system failure, this component may be less than predicted. In sepsis, certain variables such as volume of distribution and protein binding can be altered. There is a paucity of data about drug dosing during CRRT in critically ill patients. One important principle to remember is that elimination is continuous; therefore, most drugs will need to be given twice or thrice daily. Drug levels, when available, should be measured daily. The recommended doses for some of the more commonly prescribed antibiotics are listed in Table 48.2. These recommendations should not replace clinical judgment as clinical situations vary greatly.

TABLE 48.2 Dosing of Common Antimicrobial Agents During Continuous Renal Replacement Therapy (CRRT)

Drug	Dosing in CVVH	Dosing in CVVHD or CVVHDF

Drug	Dosing in CVVH	Dosing in CVVHD or CVVHDF
Vancomycin	LD 15-20 mg/kg, then 1 g q48h	LD 15-20 mg/kg, then 1 g q24h
Cefepime	1-2 g q12h	2 g q12h or 1 g q8h
Ceftazidime	1-2 g q12h	2 g q12h or 1 g q8h
Cefotaxime	1-2 g q12h	2 g q12h
Ceftriaxone	1-2 g q12-24h	2 g q12-24h
Imipenem-cilastatin	250 mg q6h or 500 mg q8h	250 mg q6h, 500 mg q6h, or 500 mg q8h
Meropenem	1 g q12h	1 g q12h
Ciprofloxacin	200 mg q12h	200-400 mg q12h
Metronidazole	500 mg q8h	500 mg q8h
Piperacillin-tazobactam	2.25 g q6h	3.375 g q6h
Amikacin	LD 10 mg/kg, then 7.5 mg/kg q24-48h	LD 10 mg/kg, then 7.5 mg/kg q24-48h
Tobramycin	LD 3 mg/kg, then 2 mg/kg q24-48h	LD 3 mg/kg, then 2 mg/kg q24-48h
Gentamicin	LD 3 mg/kg, then 2 mg/kg q24-48h	LD 3 mg/kg, then 2 mg/kg q24-48h
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
Linezolid	600 mg q12h	600 mg q12h
Fluconazole	200-400 mg q24h	400-800 mg q24h
Acyclovir	5-7.5 mg/kg q24h	5-7.5 mg/kg q24h

CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; LD, loading dose.

Drug Dosing During Prolonged Intermittent Renal Replacement Therapy

There is limited data on drug clearance and appropriate drug dosing in patients undergoing PIRRT. The same factors affecting drug dosing in CRRT are applied here. However, drug clearance is more unpredictable due to the intermittent nature of PIRRT. It is also difficult to make general dosing recommendations for a particular drug as the half-life can be quite variable during PIRRT, due to lack of uniformity in dialyzer membrane, blood, and dialysate flow rates (machine and center dependent). For once-a-day medications, the dose should be given post-PIRRT. For twice-a-day medications, the first dose should be given post-PIRRT and the second dose 12 hours later. Ideally, the PIRRT treatment should be initiated around the same time every day. Close communication between the nephrology team, the pharmacist, and the ICU team is essential to ensure adequate drug dosing.

Complications of Renal Replacement Therapy

As with any procedure, there are certain complications and adverse events that can be associated with renal replacement therapies. Vigilance for such complications and their immediate rectification are essential to prevent life-threatening situations, especially in the vulnerable population of the ICU. In addition, the necessity for a central venous catheter places the patient at risk for infectious complications.

HYPOTENSION

Intradialytic hypotension can occur in all clinical settings with all modalities, although it is more commonly seen with IHD. Patients experiencing volume depletion and sepsis are at heightened risk, and careful attention to the physical examination inclusive of serial point-of-care ultrasonography and invasive hemodynamic monitoring when indicated can help ensure adequate volume resuscitation before initiating the dialysis session. Other factors can also result in intradialytic hypotension. The rapid clearance of uremic solutes can lower the serum osmolality and lead to a fluid shift toward the intracellular space, depleting the intravascular volume. A normal saline bolus of 250 mL or administration of 25% albumin in 100 mL can be used as initial management steps in the treatment of intradialytic hypotension, and ultrafiltration may need to be turned off. The dialysate temperature can be decreased to promote vasoconstriction. Patients who are persistently hypotensive may need to switch to a continuous modality. Air embolism is a very rare complication of dialysis that can lead to hemodynamic instability. Other differential diagnoses to consider include internal hemorrhage, pericardial tamponade, and myocardial infarction.

ARRHYTHMIAS

Cardiac arrhythmias can occur in the setting of rapid electrolyte shifts in acute hemodialysis. The removal of certain antiarrhythmic drugs during dialysis is also a risk factor. In chronic dialysis, a bath with a potassium concentration of 2 to 3 mEq/L is frequently used. However, when hyperkalemia necessitates a dialysate with a potassium concentration of 0 to 1 mEq/L, it is important to monitor hourly potassium levels. A low-potassium dialysate should not be used longer than 1 hour unless the serum potassium remains critically elevated. Patients on digitalis are especially sensitive to hypokalemia. Supraventricular arrhythmias can also be triggered during the placement of the dialysis catheter, by a malpositioned dialysis catheter, and sometimes during dialysis. If the arrhythmia results in hemodynamic compromise, then therapy is discontinued immediately and cardioversion should be attempted.

DIALYZER REACTIONS

Dialyzer reactions are rare during hemodialysis. Type A, or anaphylactic, reactions are estimated to occur in 4 of every 100,000 sessions and present in the first few minutes once the blood in the circuit returns to the patient. Symptoms are varied and may include urticaria, flushing, chest pain, back pain, dyspnea, vomiting, and chills. Severe cases can progress to hypotension, cardiac arrest, and death. The cause for this reaction is believed to be related to residual amounts of ethylene oxide, which is used to sterilize dialyzers. Type A reactions are treated by immediately discontinuing the dialysis session and discarding the blood in the circuit. Further therapy with epinephrine or bronchodilators depends on the severity of the reaction.

Type B reactions are more common and are distinguished from type A reactions in that they are usually less severe and present later, usually after the first 15 minutes of dialysis. They are thought to be due to the use of unsubstituted cellulose dialyzer membranes and complement activation. They occur in 3% to 4% of sessions and also present with chest pain, back pain, dyspnea, or gastrointestinal symptoms. If the symptoms are not severe, then dialysis is continued and the symptoms slowly resolve. Treatment is supportive, with appropriate use of intravenous saline, analgesics, and antihistamines.

DIALYSIS CATHETER-RELATED PROBLEMS

The dialysis catheter itself can also pose problems. When needed acutely, a nontunneled catheter can be inserted into a central vein at the bedside. When infection and bacteremia occur, prompt catheter removal is generally recommended unless vascular access is especially difficult. Thrombus or fibrin sheaths can form around or inside the catheters causing inadequate blood flow for dialysis. Even though heparin is usually instilled into the hub of the catheter after each dialysis, this does not necessarily prevent the clot formation. An attempt at clot lysis can be made by instilling 1 to 2 mg of

alteplase into each catheter lumen. The catheter is then capped for 2 to 3 hours and the medication is aspirated before dialysis is again attempted. Alteplase should not be administered systemically for this purpose. If the catheter continues to malfunction, it should be replaced completely and not over guidewire.

In patients with CKD, subclavian veins are not used for dialysis catheters, as there is a high risk of subclavian venous stenosis, which can prevent the future placement of an arteriovenous fistula or graft in that extremity for dialysis. There are no data to suggest that tunneled catheters are more beneficial regarding infection rates or adequacy of dialysis in intensive care patients with AKI. Tunneled catheters are typically used in patients with multiple malfunctioning temporary catheters, poor chance for early renal recovery, or for those being transferred out of the ICU to a different facility. For clotted tunneled catheters, interventional radiology consultation is required to perform endoluminal brushing to dislodge thrombi and fibrin sheaths.

PROBLEMS ASSOCIATED WITH CONTINUOUS RENAL REPLACEMENT THERAPY

One of the advantages of CRRT over IHD is that the slower blood flow rates place a gentler hemodynamic burden on unstable patients. However, hypotension can still occur in this group, especially when high ultrafiltration rates are attempted. Some adverse events are specific to continuous modalities, mostly related to electrolyte abnormalities. Uninterrupted high-flow CRRT can cause dramatic hypophosphatemia, hypokalemia, and hypomagnesemia. Serum electrolytes need to be monitored at least daily. Hypokalemia can be corrected by increasing the potassium concentration in the replacement fluid and dialysate. Hypophosphatemia and hypomagnesemia can be corrected by supplementation.

Given its lower flow rates, CRRT usually requires some form of anticoagulation to prevent clotting in the extracorporeal circuit. Heparin is the preferred anticoagulant at many institutions. In cases of heparin-induced thrombocytopenia, a direct thrombin inhibitor,

argatroban or bivalirudin, can be used. When systemic anticoagulation is contraindicated, citrate can be used regionally in the dialysis circuit. Citrate chelates calcium in the serum and inhibits activation of the coagulation cascade. Citrate is quickly metabolized to bicarbonate in the liver and thus does not result in systemic anticoagulation. Calcium is replaced through a separate central venous line and this process requires close monitoring of serum-ionized calcium levels. With the breakdown of citrate to bicarbonate, the development of a metabolic alkalosis is another concern with this form of anticoagulation. Metabolic alkalosis can be treated by changing the replacement fluid to normal saline from a bicarbonate-based product.

Hypothermia is a well-known complication of CRRT and is common at high-flow rates. Significant amounts of heat are lost from the slow-flowing extracorporeal circuit and can cause drops in body temperature of 2 to 5 °C. This can be addressed by ensuring the use of warmers on CRRT devices, which either warm the dialysate or replacement fluid or warm the venous return tubing. However, this poses a problem regarding the detection of fever. Unpublished reports have shown no advantage to checking routine cultures; therefore, reliance on the other clinical signs of infection is needed.

Discontinuation of Renal Replacement Therapy

RRT should be continued until patients show evidence of renal recovery. This can be assessed by a decrease in the creatinine after a steady state in a patient with oliguria or increase in urine output in a nonoliguric patient. If there is uncertainty regarding the extent of renal recovery, a 24-hour urine collection for creatinine clearance (CrCl) can be obtained. In most patients, RRT can be discontinued if CrCl is above 15 to 20 mL/min. There are two ongoing trials examining the appropriate timing of stopping RRT in patients with AKI.

Summary

RRT is initiated when more conservative medical management has failed to control the fluid, electrolyte, and metabolic complications of AKI. Several modalities are available to the clinician, and selection between intermittent and continuous forms depends on the availability at the institution, the patient's hemodynamic stability, and comorbid illnesses. Despite the overall safety of these procedures, complications and adverse events can occur, requiring meticulous attention and, in some cases, frequent laboratory monitoring to anticipate and prevent their occurrence.

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SECTION XII HEPATIC DISEASES

49 Acute Liver Failure

Lolwa Al-Obaid and Jeffrey S. Crippin

Acute liver failure (ALF) is characterized by coagulopathy, encephalopathy, and severe hepatic injury in patients without chronic liver disease (Table 49.1). Exceptions to the absence of preexisting liver disease include autoimmune hepatitis, reactivation of hepatitis B, and Wilson disease, if the disease has only been recognized within the last 26 weeks. Approximately 2,000 cases of ALF are reported per year in the United States.

TABLE 49.1 Diagnosis and Causes of Acute Liver Failure

1. Acute hepatic injury <26 wk without evidence of preexisting liver disease
2. Encephalopathy
3. Coagulopathy (INR ≥1.5)

↓

Etiology	History and Physical Examination	Diagnostic Evaluation
Acetaminophen	History of ingestion	Acetaminophen level (short half-life-low serum level does not rule out ingestion), use nomogram when time of ingestion known
Drug toxicity	New medications, antibiotics, NSAIDs, anticonvulsants, psychiatric history, herbals; unlikely if >1 y on medication	Serum drug levels
Other toxins	Mushroom ingestion, cocaine or MDMA use	Urine drug screen

Viral	Viral syndrome, pregnancy, recent travel, skin lesions, immunocompromised state	Hepatitis B surface antigen, hepatitis B core IgM, hepatitis A IgM, hepatitis E antibody, hepatitis C antibody, hepatitis C RNA, HIV antibody, HSV antibodies and DNA, VZV DNA; consider evaluation for rare viral causes including parvovirus B19, adenovirus, and EBV
Shock liver	History of heart failure, cardiac arrest, volume depletion, or substance abuse	BNP, lactate dehydrogenase, lactate, echocardiogram
Infiltrative malignancy	History of malignancy, hepatomegaly	If suspected, cross-sectional abdominal imaging and liver biopsy (if feasible)
Budd-Chiari syndrome	History of malignancy or other prothrombotic condition, including recent pregnancy or exogenous estrogens; personal or family history of venous thromboembolism; lymphadenopathy	Abdominal ultrasound with Doppler
Wilson disease	Patient <40 y old, history of neuropsychiatric symptoms; Kayser-Fleischer rings on slit lamp exam	Serum ceruloplasmin and copper, 24-h urine copper, uric acid, hemolysis labs; if suspected, liver biopsy (if feasible) for quantitative copper measurement
Acute fatty liver of pregnancy, HELLP	Pregnancy	B-HCG in women of childbearing potential; if suspected, urinalysis to evaluate for proteinuria. If liver biopsy performed, frozen section needed for *oil red O* stain (AFLP)
Autoimmune Hepatitis	History of other autoimmune diseases	Antinuclear antibody, antismooth muscle antibody, anti-LKM1, serum immunoglobulins; if suspected, liver biopsy (if feasible)

AFLP, acute fatty liver of pregnancy; B-HCG, beta-human chorionic gonadotropin; BNP, B-type

natriuretic peptide; EBV, Epstein-Barr virus; HELLP, hemolysis, elevated liver enzyme levels, and a low platelet count; HSV, herpes simplex virus; IgM, immunoglobulin M; INR, international normalized ratio; LKM1, liver kidney microsomal antibody1; MDMA, 3,4-methylenedioxy methamphetamine; NSAID, nonsteroidal anti-inflammatory drug; VZV, varicella-zoster virus.

Causes and Diagnosis

Determining the cause of ALF is imperative, since some etiologies dictate specific treatments. In a prospective multicenter study of 308 patients (1998-2001) by the Acute Liver Failure Study Group, the following causes were most frequently identified: acetaminophen overdose (39%), indeterminate (17%), idiosyncratic drug reactions (13%), and viral hepatitis (hepatitis A virus or hepatitis B) (11%). Table 49.1 outlines the possible causes of ALF, as well as the studies needed to evaluate patients for each etiology. On presentation, initial laboratory analysis should include a complete blood count, basic metabolic panel, liver chemistries, magnesium, phosphate, prothrombin time, lactic acid, arterial blood gas, ammonia, acetaminophen level, acute viral hepatitis panel, toxicology screen, ceruloplasmin level, antinuclear antibodies, antismooth muscle antibodies, HIV status, and a pregnancy test (if applicable).

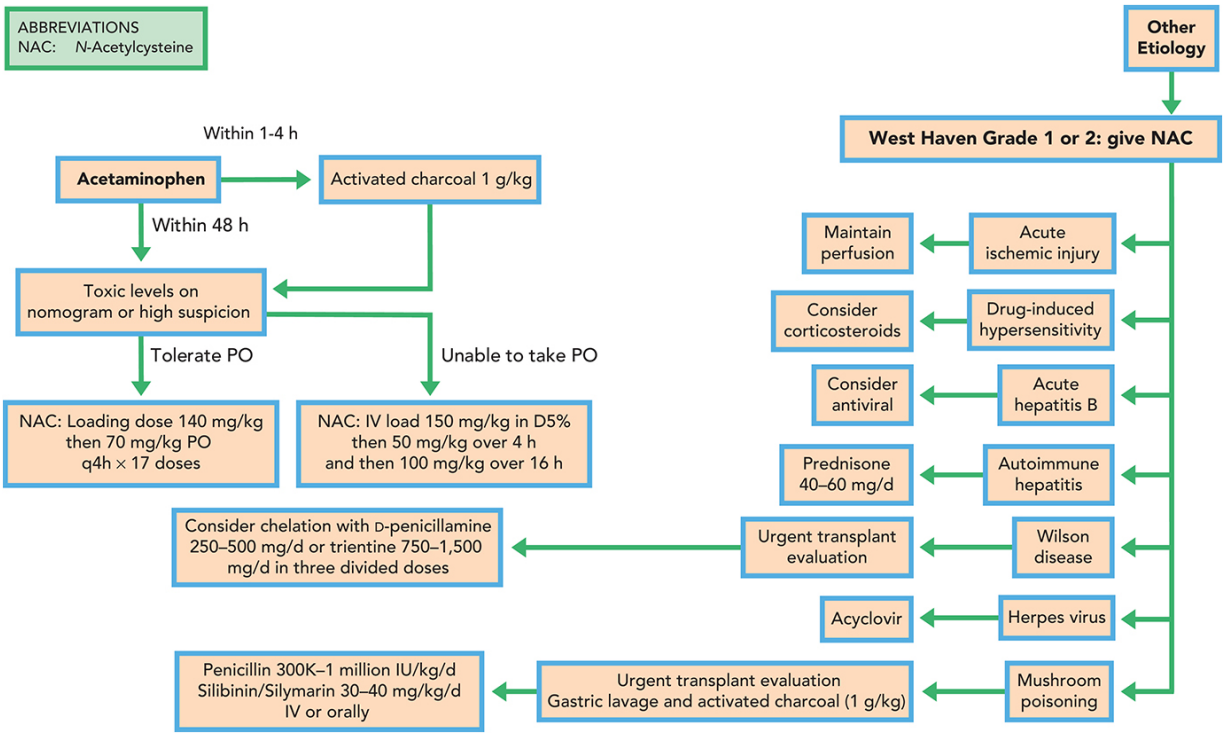
Etiology-Specific Management of Acute Liver Failure

ACETAMINOPHEN TOXICITY

As acetaminophen toxicity is the leading cause of ALF in the United States, clinicians should have a high index of suspicion for acetaminophen overdose, particularly when there is inadequate knowledge of the circumstances preceding a patient's presentation to the hospital. ALF can occur even with doses as low as 3 to 4 g/d, particularly in patients with chronic alcohol use or poor nutrition, due to depleted glutathione stores. Laboratory evaluation will usually

demonstrate markedly elevated serum aminotransferases and normal or minimally elevated bilirubin. In addition, lactic acidosis, acute kidney injury, and hypoglycemia may occur. *N*-Acetylcysteine (NAC) therapy is indicated when acetaminophen-related ALF is known or suspected, regardless of the grade of encephalopathy, and should be initiated promptly after acetaminophen ingestion (Algorithm 49.1). The nomogram shown in Chapter 36, Figure 36.1 helps to guide treatment based on the serum acetaminophen level when a single ingestion occurred at a known time. However, in the setting of ALF, treatment with NAC should be initiated if the serum acetaminophen is elevated at any level, as significant liver injury can result from multiple relatively small doses over time. If ingestion is known to have occurred within 4 hours of presentation, activated charcoal lowers the plasma acetaminophen level more effectively than does gastric lavage or ipecac, and is typically given as a single dose (1 g/kg). The efficacy of NAC is not reduced by prior treatment with activated charcoal. Patients with acetaminophen toxicity should be treated with NAC even if they present to medical care after a significant delay. A retrospective study including patients who began NAC 10 to 36 hours after overdose showed improved outcomes in this group, compared to those receiving no antidote. Refer to Algorithm 49.1 for PO and IV NAC dosing. The route of administration (oral or intravenous) has not been shown to affect outcomes. Cochrane analysis of one prospective, controlled trial of NAC for acetaminophen-related ALF showed reduced mortality (Peto odds ratio 0.29) in patients treated with NAC.

ALGORITHM 49.1 Treatment Algorithm for Acute Liver Failure


ABBREVIATIONS
NAC: N-Acetylcysteine
Other Etiology
West Haven Grade 1 or 2: give NAC
Within 1-4 h
Acetaminophen
Activated charcoal 1 g/kg
Within 48 h
Toxic levels on nomogram or high suspicion
Tolerate PO
Unable to take PO
NAC: Loading dose 140 mg/kg then 70 mg/kg PO q4h × 17 doses
NAC: IV load 150 mg/kg in D5% then 50 mg/kg over 4 h and then 100 mg/kg over 16 h
Maintain perfusion
Acute ischemic injury
Consider corticosteroids
Drug-induced hypersensitivity
Consider antiviral
Acute hepatitis B
Prednisone 40–60 mg/d
Autoimmune hepatitis
Consider chelation with D-penicillamine 250–500 mg/d or trientine 750–1,500 mg/d in three divided doses
Urgent transplant evaluation
Wilson disease
Acyclovir
Herpes virus
Penicillin 300K–1 million IU/kg/d
Silibinin/Silymarin 30–40 mg/kg/d IV or orally
Urgent transplant evaluation
Gastric lavage and activated charcoal (1 g/kg)
Mushroom poisoning

NONACETAMINOPHEN ETIOLOGIES

The benefit of NAC in acetaminophen toxicity has been demonstrated for decades, but its role in non–acetaminophen-related ALF has only recently been established. A randomized placebo-controlled trial including 173 patients with non–acetaminophen-related ALF demonstrated improved transplant-free survival at 3 weeks and 1 year in patients who received 72 hours of NAC therapy. This benefit was seen only in patients with grade 1 to 2 encephalopathy but not in those with more advanced grades. Given its minimal adverse reaction profile, NAC therapy should be considered for all patients with ALF presenting with grade 1 to 2 encephalopathy. Treatment with NAC should not delay transfer to a transplant facility.

For non–acetaminophen-related causes of liver damage, etiology-specific interventions are unlikely to be lifesaving in the setting of ALF; rather, the decision regarding the need and eligibility for liver transplant is crucial. Nonetheless, when a specific etiology is identified, initiation of directed therapy can be considered as outlined

in Algorithm 49.1. Hepatitis B, with or without hepatitis D, accounts for more than half of the viral causes of ALF. Treatment with a nucleotide or nucleoside analogue is generally recommended, though the evidence is mixed with regard to its impact on clinical outcomes in this setting; lamivudine (100 mg/d) has been used in the majority of reports. Hepatitis E is a more common viral cause of ALF in endemic countries and should be considered in returning travelers or recent immigrants from these regions. Treatment for acute hepatitis A and E is supportive. Hepatitis C alone rarely causes ALF. Other viruses such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), adenovirus, and parvovirus B19 have been reported.

Management of Systemic Complications

CENTRAL NERVOUS SYSTEM

Cerebral edema and increased intracranial pressure (ICP) are serious complications of ALF. The risk of cerebral edema increases with progression of encephalopathy, with a greater than 75% incidence in patients with grade 4 encephalopathy. Advanced cerebral edema can lead to uncal herniation and death.

Management of neurologic complications is outlined in Algorithm 49.2. Patients with any degree of encephalopathy should be transferred to a liver transplant center. Patients with grades 3 to 4 encephalopathy should be intubated for airway protection and for the purpose of inducing hyperventilation to a $Paco_2$ of 28 to 30 mm Hg. Frequent neurologic examinations are imperative, and findings such as systemic hypertension, bradycardia, posturing, and decreased pupillary reflexes can suggest impending herniation.

ALGORITHM 49.2 **CNS Complications of Acute Liver Failure**

General considerations

- CT head to rule out hemorrhage
- Elevate head of bed 30°, avoid Valsalva, avoid stimulation, sedation
- Grade III–IV encephalopathy: intubate

Consider invasive ICP monitoring; consider FVIIa for placement.

Goal ICP <20–25 mm Hg, CPP >50–60 mm Hg

Increased intracranial pressure?

ICP monitoring: ICP >20–25, CPP <50–60
Cushing reflex, irregular respirations, dilated pupils, decerebrate posturing

Intervention	Administration	Comments
Mannitol	Bolus 0.5-1 g/kg; can repeat twice at 4-6 h intervals.	No proven role in prophylaxis Keep serum osmolality <320 mOsm/kg Side effects: hypernatremia, volume overload
Hypertonic saline	30% NaCl 5-20 mL/h (titrated to achieve serum sodium 145-155 mmol/L)	May only apply to patients on renal replacement therapy
Sedation	Propofol infusion *Alternatives*: thiopental, pentobarbital	Side effects of barbiturates: severe hypotension, prolonged sedation
Hyperventilation	Titrate respiratory rate to P_{CO_2} 25–30 mm Hg for acute management of refractory ICH	Temporary measure; no proven role in prophylaxis
Management of body temperature	Treat fever; permit spontaneous core body temperatures 35-36 °C	No proven benefit of induced hypothermia

ABBREVIATIONS

CPP: central perfusion pressure
CT: computed tomography
ICH: intracranial hypertension
ICP: intracranial pressure

ICP monitoring should be considered for patients with rapidly progressive encephalopathy and those listed for liver transplantation. In the absence of definitive evidence of a mortality benefit, the frequency with which ICP monitoring is used varies widely among liver transplant programs. ICP can be measured with an epidural, subdural, parenchymal, or ventricular catheter. Epidural catheters generally have a lower complication rate but are less reliable. The most common complications include bleeding in the setting of coagulopathy, infection, and volume overload resulting from correction of coagulopathy. Recombinant factor VIIa has been shown to reduce the risk of intracranial hemorrhage from 10%-20% to less than 5%. The role of noninvasive ICP monitoring (using transcranial Doppler or pupillometry) has shown promise but requires further studies in patients with ALF. ICP should be maintained at a level less than 20 mm Hg, with a cerebral perfusion pressure (mean arterial pressure [MAP] minus ICP) greater than 50 mm Hg.

Once increased ICP or cerebral edema is present, aggressive measures should be undertaken to prevent herniation. Sedation, avoidance of sensory stimulation, and raising the head of the bed can be helpful. Therapies focused on decreasing cerebral edema include osmotic agents (mannitol or hypertonic saline) or decreasing cerebral blood flow (hyperventilation or hypothermia).

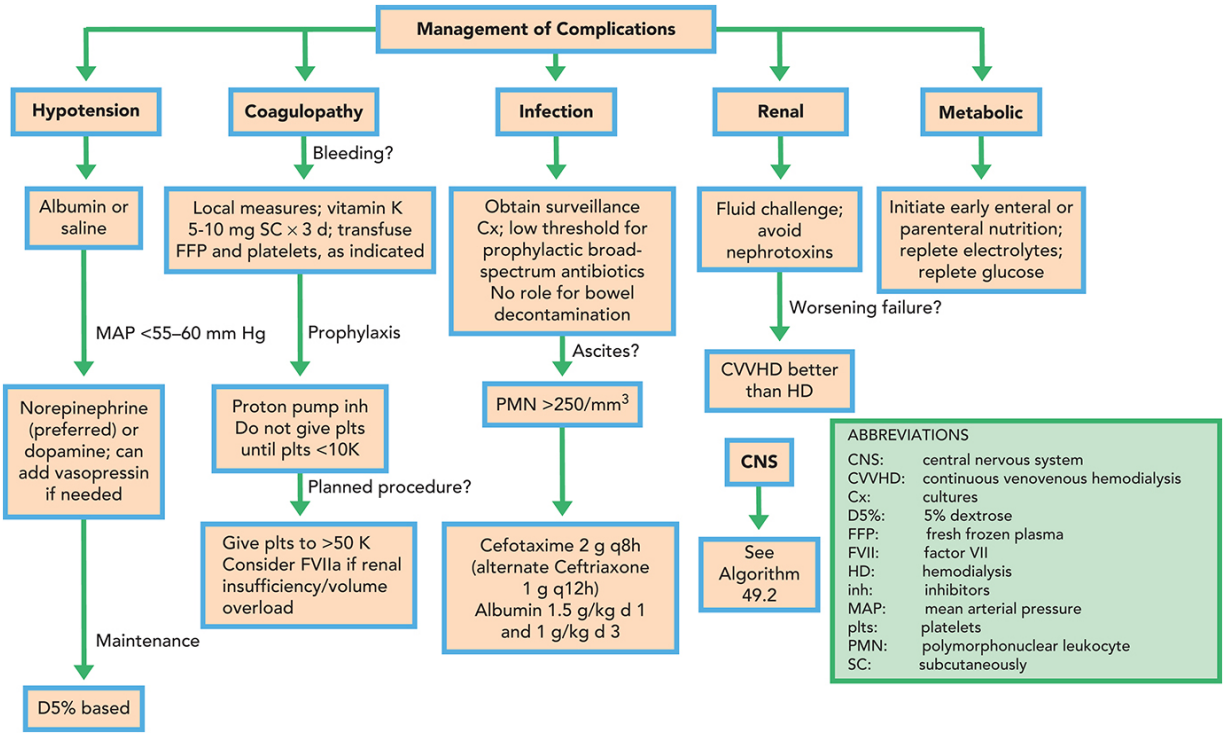
Mannitol is administered as a bolus dose (0.5-1 g/kg of a 20% solution). The dose can be repeated twice; however, administration is limited by maintaining a serum osmolality less than 320 mOsm/kg. If patients have concomitant renal failure, hemofiltration should be considered. Hyperventilation has only a short-term benefit but can be used with the goal of reducing $PaCO_2$ to 25 mm Hg. A randomized clinical trial (RCT) demonstrated no benefit of prophylactic continuous hyperventilation in ALF. A study of 30 patients with ICP monitoring randomized to 3% hypertonic saline with a goal serum sodium concentration of 145 to 155 mmol/L showed a significant decrease in average ICP and episodes of increased ICP, but no survival benefit. Hypothermia (32-34 °C) has been associated with a beneficial effect in uncontrolled trials; however, goal temperature and

rewarming protocol are not established, therefore the practice is not recommended. Patients with ALF may have seizure activity, but prophylactic phenytoin has not proven to be effective in improving survival. Despite an association between an arterial ammonia level of greater than 200 mcmol/L and herniation, no benefit of gut decontamination or lactulose has been demonstrated in ALF. Hemofiltration via continuous renal replacement therapy (CRRT) can reduce ammonia levels, though its effect on ICP has not been studied. Barbiturate coma can be attempted for refractory increased ICP but requires close monitoring of MAP due to its association with hypotension. Corticosteroids are not effective at prolonging survival or improving cerebral edema.

COAGULOPATHY

The management of coagulopathy is outlined in Algorithm 49.3. Synthesis of coagulation factors I, II, V, VII, IX, and X is depressed in patients with ALF, and lab abnormalities frequently include thrombocytopenia, hypofibrinogenemia, and abnormal clot formation on rotational thromboelastography (ROTEM). Sources of bleeding include procedure sites, stress ulcers, lungs, and the oropharynx. Proton pump inhibitors should be used for stress ulcer prophylaxis. Platelets should only be transfused for counts less than 10,000/mcL or in the face of active bleeding. Vitamin K is routinely given, but fresh frozen plasma should not be transfused unless there is active bleeding or a planned procedure. Packed red blood cells can be transfused for symptomatic anemia or to replace blood loss secondary to hemorrhage.

ALGORITHM 49.3 **Management of the Complications of Fulminant Hepatic Failure**


Management of Complications
Hypotension
Coagulopathy
Infection
Renal
Metabolic
Albumin or saline
Bleeding?
Local measures; vitamin K 5-10 mg SC × 3 d; transfuse FFP and platelets, as indicated
Obtain surveillance Cx; low threshold for prophylactic broad-spectrum antibiotics No role for bowel decontamination
Fluid challenge; avoid nephrotoxins
Initiate early enteral or parenteral nutrition; replete electrolytes; replete glucose
MAP <55–60 mm Hg
Prophylaxis
Ascites?
Worsening failure?
Norepinephrine (preferred) or dopamine; can add vasopressin if needed
Proton pump inh Do not give plts until plts <10K
PMN >250/mm3
CVVHD better than HD
Planned procedure?
CNS
Maintenance
Give plts to >50 K Consider FVIIa if renal insufficiency/volume overload
Cefotaxime 2 g q8h (alternate Ceftriaxone 1 g q12h) Albumin 1.5 g/kg d 1 and 1 g/kg d 3
See Algorithm 49.2
D5% based
ABBREVIATIONS
CNS: central nervous system
CVVHD: continuous venovenous hemodialysis
Cx: cultures
D5%: 5% dextrose
FFP: fresh frozen plasma
FVII: factor VII
HD: hemodialysis
inh: inhibitors
MAP: mean arterial pressure
plts: platelets
PMN: polymorphonuclear leukocyte
SC: subcutaneously

HYPOTENSION

Hypotension is multifactorial in patients with ALF, resulting from volume depletion, third spacing, infection, gastrointestinal bleeding, or as a result of overall low systemic vascular resistance and a hyperkinetic cardiovascular state. Fluid resuscitation should be balanced with avoidance of volume overload and the theoretical risk of increasing ICP. Maintenance fluid should be glucose based due to the hypoglycemia associated with liver failure. Although not compared directly in trials, dopamine or norepinephrine can be used for vasopressor support with a MAP goal of 65 to 75 mm Hg. In a small study, dopamine led to a significant increase in cardiac output, systemic oxygen delivery, and hepatic and splanchnic blood flow when used to increase MAP by 10 mm Hg. Although systemic oxygen consumption was increased, splanchnic oxygen consumption was decreased. A small trial evaluating the role of norepinephrine in ALF noted an increase in MAP, although it was not associated with an increase in cardiac index and actually resulted in a decrease in systemic oxygen consumption. Resuscitation with

colloid is theoretically better than crystalloid, given that albumin induces a more effective expansion of the central blood volume, but no mortality benefit has been shown.

INFECTION

Infections are found in 80% of patients with ALF, with 25% of patients developing documented bacteremia and 33% developing systemic fungal infections. Periodic surveillance cultures should be obtained to detect infections as early as possible as infection may preclude liver transplantation. Although prophylactic antibiotics do not provide a survival advantage, a low threshold for initiation of broad-spectrum coverage should be maintained, particularly in patients awaiting liver transplantation. Infections and hyperthermia increase the risk of hepatic encephalopathy; therefore, a theoretical benefit of empiric antibiotic therapy exists for patients with worsening encephalopathy.

RENAL FAILURE

Renal failure is multifactorial in patients with ALF because of the direct toxic effect of ingested substances, volume depletion, hypotension, acute tubular necrosis, and the hepatorenal syndrome. In contrast to acute tubular necrosis, renal failure due to the hepatorenal syndrome is characterized by low urinary sodium (<10 mEq/L), progressive hyponatremia, and a lack of improvement with volume expansion. Nephrotoxic agents such as aminoglycosides and nonsteroidal anti-inflammatory drug (NSAIDs) should be avoided, and NAC should be used before intravenous contrast studies. When dialysis is needed, continuous renal replacement therapy should be used over daily intermittent hemodialysis, due to its association with improved cardiovascular dynamics.

METABOLIC COMPLICATIONS

Metabolic complications include hypoglycemia resulting from diminished glucose synthesis and lactic acidosis due to anaerobic

glucose metabolism. Patients benefit from glucose monitoring and treatment of hypoglycemia with dextrose-based solutions. Electrolytes such as phosphorus, potassium, and magnesium are usually abnormal and should be repleted as indicated. Enteral or parenteral nutrition should be initiated early, and protein should not be restricted. A recent Cochrane database review did not find convincing evidence of a beneficial role of branched-chain amino acids in the treatment of patients with hepatic encephalopathy.

Prognostic Indicators

The most important prognostic indicator in ALF is the etiology of hepatic damage. Acetaminophen toxicity, hepatitis A, ischemic liver injury, and pregnancy-related liver failure portend a transplant-free survival of greater than 50%, while idiosyncratic drug reactions, hepatitis B, autoimmune hepatitis, Wilson disease, and Budd-Chiari Syndrome carry a survival rate of less than 25% without transplantation. The timing of disease onset is also important, but this data may be confounded by the etiology of ALF. An illness of less than 1 week in duration suggests ischemic hepatopathy or acetaminophen overdose and is associated with improved survival, while an illness greater than 4 weeks in duration suggests an indeterminate or viral etiology and indicates a poor transplant-free survival. The degree of encephalopathy as determined by the West Haven criteria is another strong predictor of outcome (Table 49.2). Patients with grade 2 encephalopathy have a 65% to 70% chance of survival, whereas patients with grade 3 or 4 have a 30% to 50% and a 20% chance of survival, respectively. The King's College Criteria (Table 49.3) are important indicators of outcome. In patients with non–acetaminophen-associated ALF, the presence of a single factor is associated with a mortality rate of 80%, while the presence of all three factors is associated with 95% mortality. In patients with acetaminophen hepatotoxicity and ALF, a single risk factor is associated with a mortality of 55%, and the presence of severe acidosis confers 95% mortality.

TABLE 49.2 West Haven Criteria for Semiquantitative Grading of Mental State

Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
Grade 3	Somnolence to semistupor but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Reprinted by permission from Springer: Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. *Am J Dig Dis*. 1978;23(5):398-406.

Liver Transplantation

Liver transplantation is a proven treatment for ALF and is indicated when prognostic indicators predict a high likelihood of death, although limited by the prompt availability of donors. Posttransplant survival rates are as high as 80% to 90%. Factors to consider include the possibility of spontaneous recovery, the feasibility of transplantation, and the assessment of contraindications to transplantation. Prognostic models such as the King's College Criteria (Table 49.3) and the Acute Physiology and Chronic Health Evaluation (APACHE) II score help in determining the need for liver transplantation. For patients with acetaminophen-associated ALF, King's College Criteria was found to have a sensitivity of 0.59 and a

specificity of 0.92 in determining the need for transplantation. An APACHE II score of greater than 15 was associated with a specificity of 0.81 and sensitivity of 0.92 in determining the need for transplantation. Although deceased donor liver transplantation is the primary source of donor grafts, living donor liver transplantation can be considered given the potential for a lack of available donor organs. However, there is controversy regarding the use of live donation due to concern of undue pressure on the donor. In addition, the urgency with which evaluations have to be performed increases the risk of an incomplete evaluation. Auxiliary partial orthotopic liver transplantation, a technique that involves resection of part of the native liver and replacement with the corresponding part of a donor liver, has shown promise in this population as well.

TABLE 49.3 King's College Hospital Criteria for Liver Transplantation in Fulminant Hepatic Failure

Acetaminophen-induced disease	Arterial pH <7.30 OR Prothrombin time >100 s AND Creatinine >3.4 mg/dL AND Grade III or IV encephalopathy
Nonacetaminophen-induced disease	Prothrombin time >100 s (regardless of encephalopathy grade) OR Any three of the following (regardless of encephalopathy grade): Age <10 y or >40 y Etiology: non-A, non-B hepatitis, halothane hepatitis, or idiosyncratic drug reaction Duration of jaundice before onset of encephalopathy >7 d Prothrombin time >50 s Serum bilirubin >18 mg/dL

From O'Grady JG, Alexander GJ, Kayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97(2):439-445.

50 Hyperbilirubinemia

Parth Shah and Jeffrey S. Crippin

Physiology

Heme is a breakdown constituent of senescent erythrocytes. It is converted to biliverdin by heme oxygenase and further reduced by biliverdin reductase to bilirubin in the reticuloendothelial system. Bilirubin, unconjugated and water insoluble at this point, is tightly bound to albumin and delivered to the liver. It is transported into the hepatocytes by carrier-mediated mechanisms, transferred to the endoplasmic reticulum bound by cytosolic proteins, and converted to a water-soluble form with the addition of uridine diphosphate glucuronic acid. This is now the conjugated form of bilirubin. An adenosine triphosphate (ATP)-dependent export pump then transfers conjugated bilirubin into the biliary canaliculi, where it is added to bile. Bile eventually drains into the small intestine and is subsequently metabolized by ileal and colonic bacteria to urobilinogen. Eighty percent of urobilinogen is excreted in stool, while approximately 20% is reabsorbed in the small intestine and enters the portal circulation. The reabsorbed urobilinogen is subsequently excreted in stool and urine.

Based on the physiology mentioned earlier, the bilirubin pathway can be divided into four steps: (1) bilirubin production, (2) hepatic bilirubin uptake, (3) bilirubin conjugation, and (4) bilirubin excretion. Hyperbilirubinemia is classically divided into unconjugated and conjugated forms. Disruption at steps 1, 2, or 3 can lead to unconjugated hyperbilirubinemia whereas disruption of step 4 can cause conjugated hyperbilirubinemia. However, this division is rarely absolute and clinicians may encounter a mixed picture.

INDIRECT HYPERBILIRUBINEMIA

Indirect hyperbilirubinemia occurs when unconjugated bilirubin is more than 80% of the total bilirubin. This may be caused by increased bilirubin production or a decrease in hepatocyte uptake and conjugation (due to inhibition of uptake mechanisms, inhibition of glucuronidation, or defects in conjugation). Hemolysis, extravasation of blood into tissues (resorption of internal bleeding or hematoma), dyserythropoiesis (thalassemia, sickle cell anemia, myelodysplasia, aplastic anemia, vitamin B_{12}, folate deficiency, or red blood cell enzyme disorders), hereditary disorders of conjugation, drug-induced effects, and sepsis are the main causes of unconjugated hyperbilirubinemia. Hemolysis is frequently characterized by an elevated reticulocyte count, schistocytes or spherocytes on peripheral smear, a positive Coombs test, an increased lactate dehydrogenase, and a decreased haptoglobin level which produces large amounts of bilirubin that overwhelm the conjugation pathway.

In addition, competitive inhibition of bilirubin uptake can also lead to indirect hyperbilirubinemia and may be caused by medications such as rifampin or probenecid, while inhibition of glucuronidation can occur with hyperthyroidism and estradiol therapy. A common enzymatic defect, decreased activity of bilirubin Uridine diphosphate (UDP)-glucuronyl transferase, results in asymptomatic unconjugated hyperbilirubinemia, better known as Gilbert's syndrome. A more severe and rare quantitative defect in UDP-glucuronyl transferase leads to Crigler-Najjar types I and II.

DIRECT HYPERBILIRUBINEMIA

Direct or conjugated hyperbilirubinemia is usually secondary to hepatocellular dysfunction, intrahepatic cholestasis, biliary obstruction, or biliary injury. Hepatocellular dysfunction, whether acute or chronic, can cause reflux of conjugated bilirubin into the circulation. This is dependent largely on the fact that active canalicular excretion of conjugated bilirubin is the rate-limiting step in

the bilirubin pathway and extremely sensitive to liver dysfunction. Acute hepatocellular dysfunction is characterized by an elevated bilirubin in association with elevated aminotransferases. Chronic dysfunction results in lower aminotransferase levels and common causes include chronic viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH). Both acute and chronic liver dysfunction may give rise to mixed hyperbilirubinemia if a disease process causing unconjugated hyperbilirubinemia is superimposed on hepatic dysfunction.

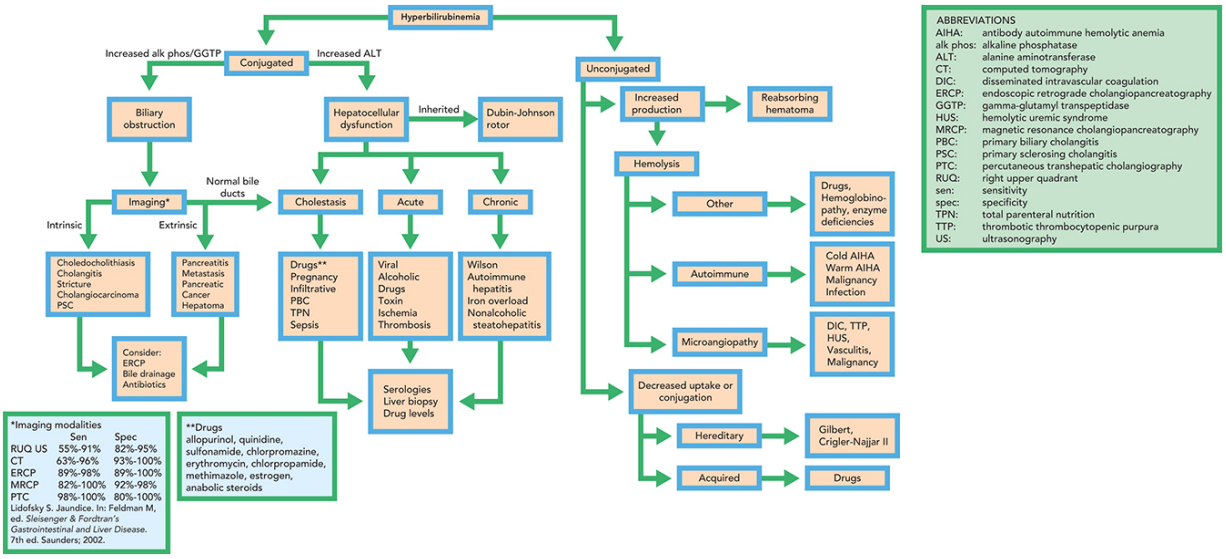
Direct hyperbilirubinemia may also result from obstruction of the extrahepatic biliary ducts or nonobstructive injury of the intra- or extrahepatic ducts. A direct bilirubin fraction more than 50% of the total bilirubin suggests a hepatobiliary etiology and, if accompanied by an elevated alkaline phosphatase and gamma-glutamyl transpeptidase (GGT), favors biliary obstruction. Causes of intrinsic obstruction include choledocholithiasis, biliary strictures, cholangiocarcinoma, intrahepatic malignancy, primary sclerosing cholangitis, AIDS cholangiopathy, and infection (e.g., *Cryptosporidium*, cytomegalovirus [CMV]). Extrinsic compression can be secondary to pancreatic masses (tumor, fibrosis, pseudocyst, or abscess) or lymphadenopathy. Nonobstructive and intrahepatic biliary disease also presents with an elevated alkaline phosphatase, an elevated GGT, and direct hyperbilirubinemia, but without obvious imaging evidence of obstruction. Potential etiologies include acute viral hepatitis, autoimmune disorders, primary biliary cirrhosis, infiltrative diseases such as amyloidosis and sarcoidosis, drug toxicity, pregnancy, sepsis, total parenteral nutrition, and paraneoplastic syndrome secondary to renal cell carcinoma. Other diseases such as Dubin-Johnson and Rotor syndrome can also cause direct hyperbilirubinemia.

DIAGNOSIS AND THERAPY

The physical examination should focus on signs of liver disease other than jaundice. Initial workup depends on whether the hyperbilirubinemia is conjugated or unconjugated. In addition to total

and direct bilirubin levels, a urinalysis that is positive for bilirubin suggests an increase in conjugated bilirubin (since conjugated bilirubin is water soluble and can be excreted in urine). Imaging can guide diagnosis and therapy. Imaging modalities include ultrasound, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and magnetic resonance cholangiopancreatography (MRCP) (Algorithm 50.1). An abdominal ultrasound or CT, both with high specificity, can confirm an obstructive process. Ultrasound is a more sensitive technique for detecting stones within the gallbladder, whereas both techniques are less apt to identify choledocholithiasis. An ultrasound is less helpful in patients who are obese and when overlying bowel gas is present. A CT, on the other hand, can provide more information about liver and pancreatic parenchymal disease. If these studies fail to reveal the cause of biliary obstruction, an MRCP gives better visualization of the intrahepatic ducts. If an obstructive process is confirmed, cholangiography can provide direct access to the biliary tree. An ERCP gains access to the proximal biliary tree while a percutaneous transhepatic cholangiogram (PTC), performed by an interventional radiologist, starting at the peripheral bile ducts, allows visualization of the biliary tree. ERCP allows decompression of obstructive processes via sphincterotomy and stone retrieval, stricture dilation, or stent placement. Superimposed infection of an obstructed biliary tract must promptly be treated with broad-spectrum antibiotics and decompression of the biliary tree. If no obstruction is found and a cholestatic pattern still persists, cholangiography may be useful to delineate biliary anatomy. CT imaging can reveal infiltrative disease, and a liver biopsy may be required to further aid in diagnosis by defining the amount and type of liver injury.

ALGORITHM 50.1 Evaluation and Management of Hyperbilirubinemia



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This chapter discusses common causes of biliary dysfunction and provides an approach to diagnosing biliary disease.

Lidofsky S. Jaundice. In: Feldman M, ed. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 7th ed. Saunders; 2002.

This chapter provides a systematic approach to evaluating a patient with jaundice and compares the various imaging modalities to evaluate biliary disease.

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Summerfield JA. Diseases of the gallbladder and biliary tree. In: Warrell DA, Cox TM, Firth JD, et al., eds. *Oxford Textbook of Medicine*. 4th ed. Oxford University Press; 2003.

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Wolkoff A. The hyperbilirubinemias. In: Kasper D, et al., eds. *Harrison's Principles of Internal Medicine*. 16th ed. McGraw-Hill; 2005.

This chapter provides a great review of the pathophysiology and disorders of the biliary system.

51 End-Stage Liver Disease

Lolwa Al-Obaid and Kevin M. Korenblat

The shared outcome of most untreated chronic liver diseases is the development of cirrhosis. The resulting symptomatic liver disease is commonly referred to as decompensated cirrhosis. The clinical signs and symptoms of decompensated cirrhosis arise from portal hypertension and hepatic synthetic dysfunction, which typically coexist in patients and are the major causes of liver disease–related morbidity and mortality. The most common complications of portal hypertension are ascites, gastrointestinal bleeding, hepatic encephalopathy, and acute kidney injury (AKI). Acute-on-chronic liver failure (ACLF) defines a related syndrome of hepatic decompensation and extrahepatic organ failure in one or more organs.

Ascites

Ascites describes the pathologic accumulation of serous fluid in the peritoneal cavity. It is the most frequent manifestation of decompensated cirrhosis and is associated with a median 2-year mortality rate of 50%. Cirrhotic ascites is identified by its low albumin content and a difference of greater than 1.1 g/dL between serum and ascites albumin concentrations (serum to ascites albumin gradient).

Paracentesis for sampling of the ascites is required for all patients with new-onset ascites or those with a change in their clinical condition, such as confusion, AKI, or gastrointestinal bleeding. Paracentesis (Figure 51.1) is a safe procedure that can be done even in patients with coagulopathy and thrombocytopenia. The right and left lower abdominal quadrants are preferred sites for paracentesis, and complications are unusual and mostly limited to

abdominal wall hematomas. The ascites should be analyzed for albumin, cell count with differential, and the fluid should be inoculated directly into blood culture media.

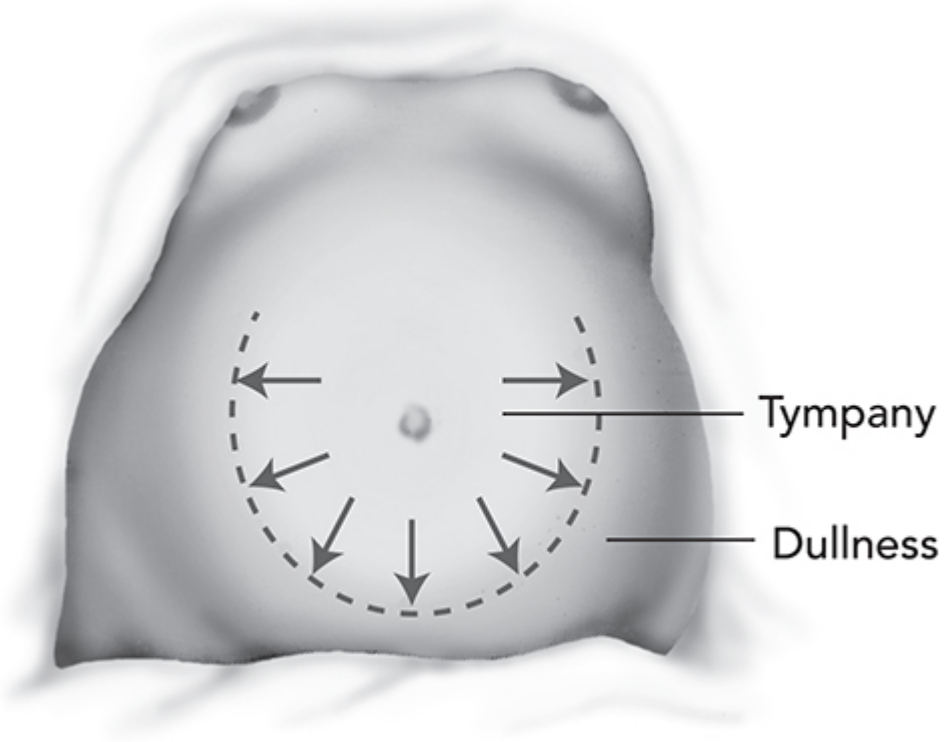


FIGURE 51.1 Areas of dullness in both right and left lower abdominal quadrants are ideal sites for diagnostic paracentesis.

Although ascites is best managed with oral furosemide and spironolactone, diuretics may need to be withheld in intensive care unit (ICU) patients with AKI, hypovolemia, or electrolyte disturbances. Intravenous (IV) diuretics for ascites and edema should be avoided in patients with cirrhosis as they can precipitate renal failure. Repeated large-volume paracentesis, defined as a paracentesis of more than 5 L, is a valid strategy for the management of ascites refractory to medical therapy. The administration of albumin at the time of paracentesis has been advocated to ameliorate the risk of postparacentesis circulatory dysfunction, which can present as AKI, including the hepatorenal syndrome, hyponatremia, or hepatic encephalopathy. In practice, 6

to 8 g of 25% albumin per liter of ascites removed can be infused. The timing of administration has not been rigorously studied but owing to the long half-life of albumin in the circulation, the administration after completion of paracentesis is likely to be sufficient.

The principal benefit of large-volume paracentesis is relief of symptoms; there is no evidence that individuals with large-volume cirrhotic ascites are at risk for the abdominal compartment syndrome. Therefore, paracentesis should not be expected to improve renal function.

Hepatic hydrothorax occurs in as many as 13% of those with ascites, typically collecting in the right hemithorax. It occurs from transdiaphragmatic passage of ascites into the pleural space through small defects in the diaphragm. The fluid of the hydrothorax typically meets Light criteria for a transudate, and the serum to pleural fluid albumin gradient is more than 1.1 g/dL. The fluid may meet criteria for an exudate when the pleural space has been subject to repeated thoracentesis or infections. In these cases, the albumin gradient can clarify the diagnosis.

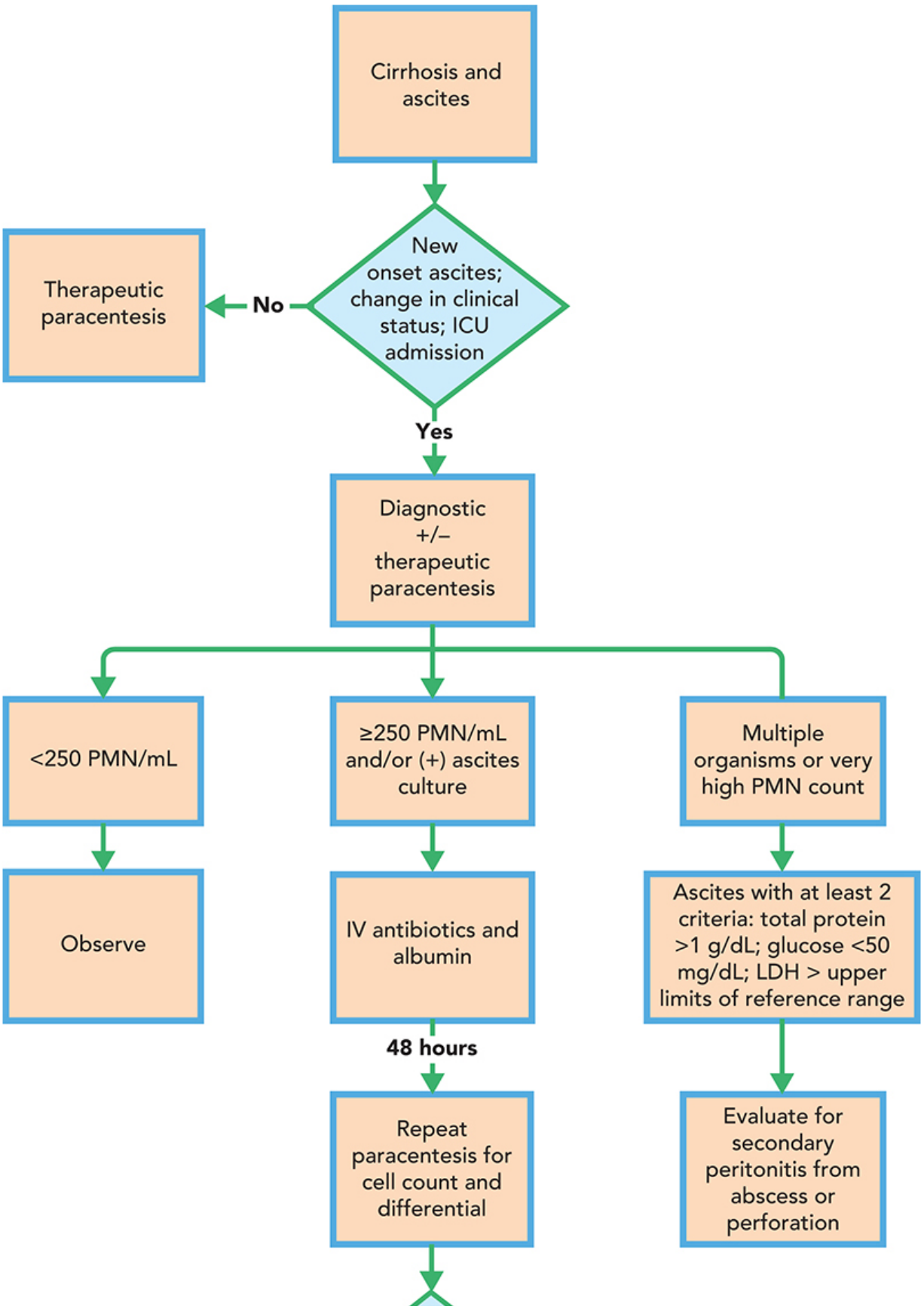
Complications of hydrothorax include spontaneous bacterial empyema, respiratory failure, trapped lung, and thoracentesis-related complications. The presence of hepatic hydrothorax is a poor prognostic indicator and has been associated with a higher mortality than that predicted by the Model for End-Stage Liver Disease (MELD) score. It can be managed by thoracentesis, diuretics, and transjugular intrahepatic shunt (TIPS) in cases refractory to medical therapy. Tube thoracostomy should be avoided because volume losses can be substantial and precipitate AKI. Hypoxemia from hydrothorax should spur evaluation for the hepatopulmonary syndrome or parenchymal lung disease.

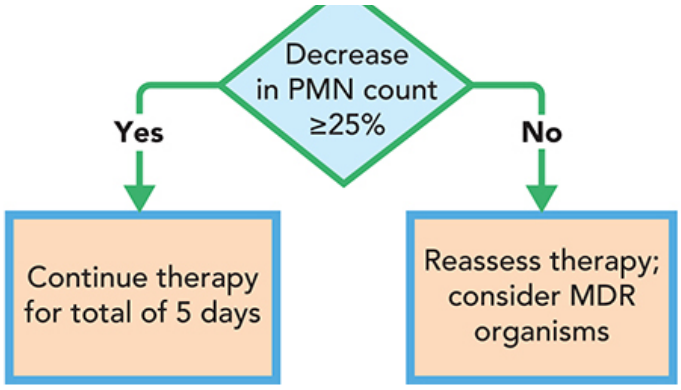
Spontaneous Bacterial Peritonitis

The most common infectious complication of ascites is the development of spontaneous bacterial peritonitis (SBP). Infections,

including SBP, are associated with a 4-fold increase in hospital mortality. Between 10% and 27% of those with cirrhotic ascites will have SBP at the time of hospitalization. There is no typical presentation of SBP, and signs such as abdominal pain, fever, or leukocytosis are frequently absent. The diagnosis is established by the finding of 250 or more polymorphonuclear (PMN) cells per milliliter in the ascites or the growth of organisms in culture of ascites fluid. SBP should be differentiated from secondary bacterial peritonitis because of bowel perforation or intra-abdominal abscess (Algorithm 51.1).

ALGORITHM 51.1 **Algorithm for the Assessment of Cirrhotic Ascites and Treatment of SBP**


Cirrhosis and ascites
New onset ascites; change in clinical status; ICU admission
No
Therapeutic paracentesis
Yes
Diagnostic +/– therapeutic paracentesis
<250 PMN/mL
≥250 PMN/mL and/or (+) ascites culture
Multiple organisms or very high PMN count
Observe
IV antibiotics and albumin
Ascites with at least 2 criteria: total protein >1 g/dL; glucose <50 mg/dL; LDH > upper limits of reference range
48 hours
Repeat paracentesis for cell count and differential
Evaluate for secondary peritonitis from abscess or perforation



Monomicrobial gram-negative organisms are the most frequent cause of SBP. Infection should be treated with IV antibiotics. Third-generation cephalosporins (ceftriaxone 1 g every 24 hours) or cefotaxime (2 g every 12 hours) are effective first-line therapies for SBP. Infections with multidrug resistant (MDR) organisms, however, are increasing. Risk factors for MDR organisms include nosocomial infections, recent hospitalization, and ICU patients. Treatment options for the failure of first-line antibiotics or suspected MDR organisms include piperacillin/tazobactam, carbapenems, and vancomycin.

Renal dysfunction occurs in as many as one-third of patients with SBP despite adequate antimicrobial treatment. Discontinuation of diuretics and the administration of IV 25% albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) reduces the rate of kidney injury. Albumin administration should be strongly considered in all patients with SBP, and particularly in those with jaundice and preexisting kidney disease. Many patients with cirrhosis are also on beta-blockers for prevention of variceal bleeding, and these medications should also be held at the time of diagnosis of SBP.

Repeat paracentesis 2 days after initiation of treatment provides evidence of response. The failure to achieve at least a 25% reduction in PMN cell counts from pretreatment levels should prompt consideration for a change from first- to second-line antimicrobial therapies.

Antibiotic prophylaxis has been advocated in patients with cirrhosis at high risk for bacterial complications. These include

patients with variceal hemorrhage, primary prevention of SBP in those with ascitic fluid protein less than 1.5 g/dL, BUN more than 25 mg/dL, serum Na less than 130 mEq/L, or bilirubin more than 3 mg/dL, or secondary prevention in those with a prior episode of SBP. Prophylactic antibiotics are less effective in patients colonized with MDR bacteria, and balancing the benefits of prophylactic antibiotics with the inevitable risks of selection for antimicrobial resistance remains the central concern with antibiotic prophylaxis.

Acute Kidney Injury

AKI in decompensated cirrhosis can arise from the depletion of intravascular volume, parenchymal renal disease, medication-related injuries, and reduction in renal perfusion from the vasodilation in mesenteric and systemic circulations, which is the hallmark of decompensated cirrhosis.

A consensus definition of AKI in cirrhosis is an increase in serum creatinine (sCR) of 0.3 mg/dL or more within 48 hours, or an increase in sCR of 1.5 times or more above baseline. The stage of AKI is defined by the magnitude of the change in sCR from baseline (Table 51.1). AKI from hepatorenal syndrome (HRS-AKI) requires kidney injury, cirrhosis with ascites, and the absence of competing diagnoses (parenchymal kidney disease, shock, nephrotoxic medication exposure).

TABLE 51.1 Diagnosis, Classification, and Stages of AKI in Patients With Cirrhosis

		HRS-NAKI	
HRS-AKI		HRS-AKD	HRS-CKD

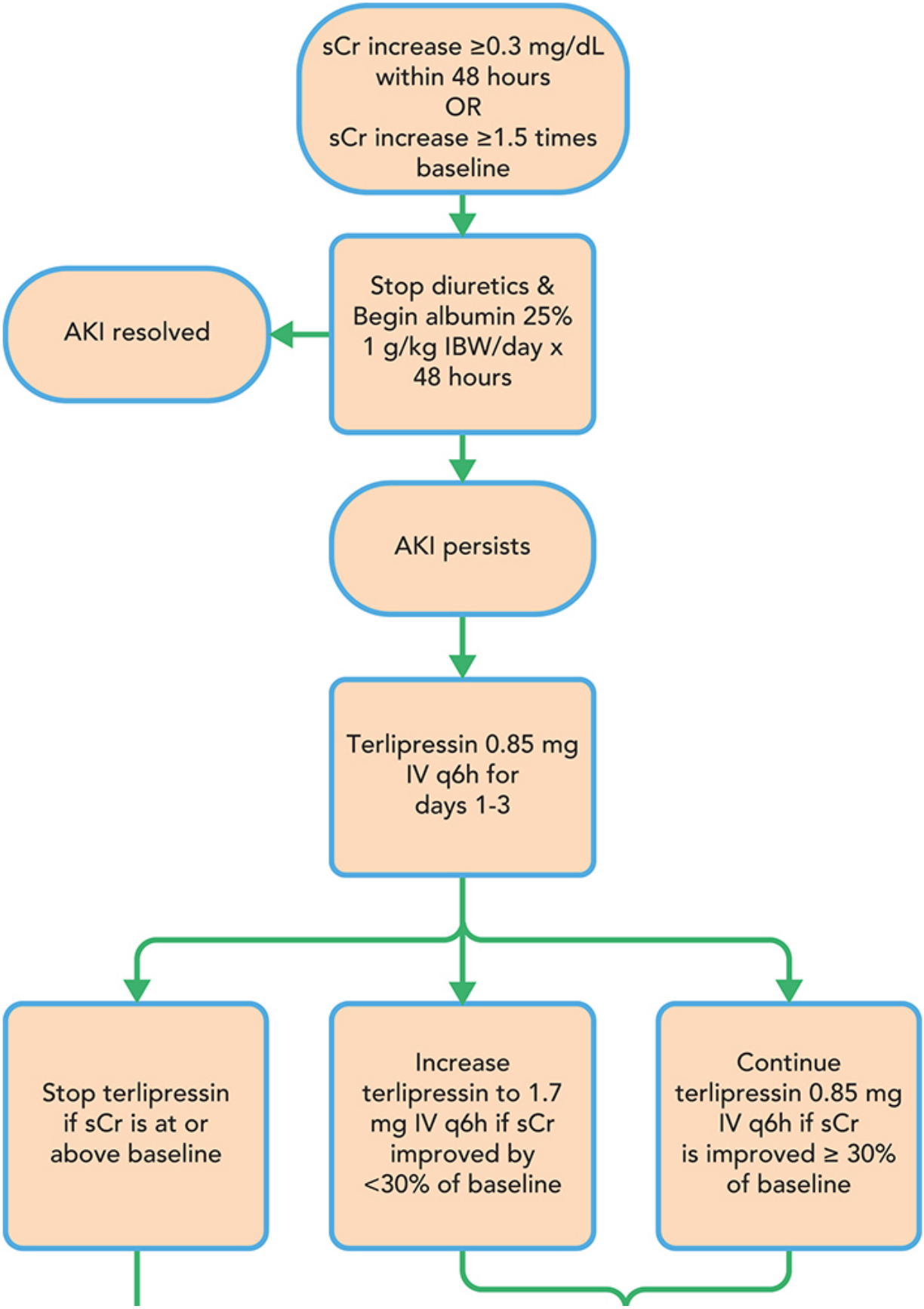
		HRS-NAKI	
	HRS-AKI	**HRS-AKD**	**HRS-CKD**
Definition	Increase in sCr ≥0.3 mg/dL within 48 h or increase in sCr ≥1.5 times baseline; no response to diuretic withdrawal and albumin 25% 1 g/kg IBW/day (48 h); cirrhosis with ascites; no shock, nephrotoxic medications, or parenchymal renal disease	eGFR <60 mL/min for <3 mo (absent other cases of kidney disease) or increase in sCR <50% of a baseline value that is within 3 mo	eGFR <60 mL/min for ≥3 mo absent other causes of kidney disease
Stages of HRS-AKI			
1a	1b	2	3
sCr <1.5 mg/dL with an increase of >0.3 mg/kg or an increase in sCr ≥1.5- to 2-fold from baseline	sCr ≥1.5 mg/dL with an increase of >0.3 mg/kg or an increase in sCR ≥1.5- to 2-fold from baseline	Increase in sCr >2- to 3-fold from baseline	Increase in sCr >3-fold from baseline or sCr 4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy

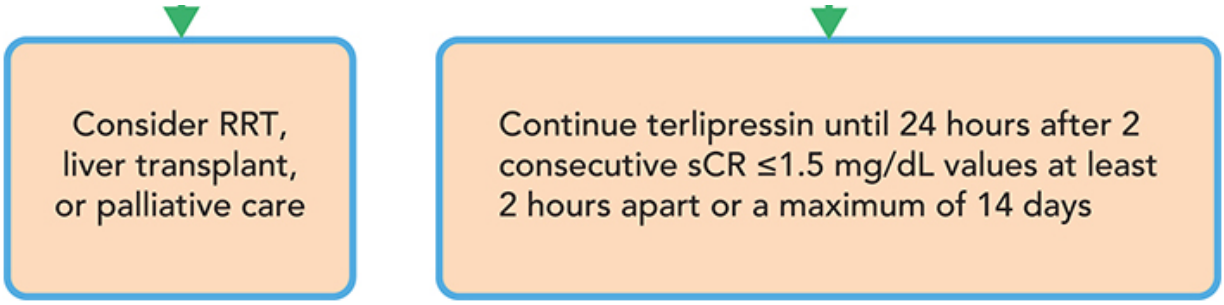
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; IBW, ideal body weight; NAKI, non–acute kidney injury; sCr, serum creatinine.

The management of HRS-AKI requires discontinuation of diuretics, volume expansion with IV 25% albumin, and, if there is no response to albumin, treatment with terlipressin, a vasopressin receptor agonist (Algorithm 51.2). Terlipressin is indicated for the treatment of

hepatorenal syndrome. The approved starting dose in the United States is 0.85 mg IV over 2 minutes every 6 hours. Treatment is given for 3 days, after which further treatment decisions are based on the creatinine response. Terlipressin is not recommended in those with a baseline sCR more than 5 mg/dL and is contraindicated in those with oxygen saturation (Spo_2) less than 90% or in those with coronary, peripheral, or mesenteric ischemia. In all cases, the earlier the intervention for HRS-AKI, the greater the likelihood of improvement. Patients with volume overload or ACLF grade 3 or higher are at increased risk of respiratory failure with terlipressin and should be closely monitored or not treated.

ALGORITHM 51.2 **Algorithm for the Management of Hepatorenal Syndrome-Acute Kidney Injury**


sCr increase ≥0.3 mg/dL within 48 hours
OR
sCr increase ≥1.5 times baseline
Stop diuretics & Begin albumin 25% 1 g/kg IBW/day x 48 hours
AKI resolved
AKI persists
Terlipressin 0.85 mg IV q6h for days 1-3
Stop terlipressin if sCr is at or above baseline
Increase terlipressin to 1.7 mg IV q6h if sCr improved by <30% of baseline
Continue terlipressin 0.85 mg IV q6h if sCr is improved ≥ 30% of baseline


Consider RRT, liver transplant, or palliative care
Continue terlipressin until 24 hours after 2 consecutive sCR ≤1.5 mg/dL values at least 2 hours apart or a maximum of 14 days

Kidney disease from HRS within or greater than 3 months duration is further defined as HRS-AKD (acute kidney disease) and HRS-CKD (chronic kidney disease), respectively.

Hepatic Encephalopathy

Early symptoms of hepatic encephalopathy are often subtle and can include changes in mood and insomnia, which later progress to agitation and coma. The development of encephalopathy of any severity should prompt a search for precipitants, which commonly include infection, gastrointestinal hemorrhage, or exposure to neuroactive medications such as benzodiazepines or opioids. The mediators of hepatic encephalopathy are unknown. Serum ammonia is a biomarker of hepatic encephalopathy but may not correlate well with its severity.

Treatment options include cathartics (lactulose 30 mL PO [per os] every 2-8 hours or lactulose retention enemas) or nonabsorbable oral antibiotics (neomycin 500 mg PO every 6 hours or rifaximin 550 mg bid [twice daily]). The bonded dipeptide L-ornithine-L-aspartate (HepatoLOLA 6 g PO TID [three times daily]) is a nonprescription nutritional supplement available as an alternative treatment for hepatic encephalopathy. The constituent amino acids in HepatoLOLA upregulate pathways that consume ammonia. The supplement is not recommended for patients with sCR more than 3 mg/dL.

Variceal Hemorrhage

Variceal hemorrhage has an annual incidence rate of 20% in cirrhosis, and each episode carries a 20% to 40% mortality rate. It can occur in those with cirrhotic and noncirrhotic portal hypertension. The initial steps in the management of acute variceal bleeding involve treatment of shock and protection of the airway from aspiration of blood (Table 51.2). Volume resuscitation in the form of packed red blood cells should be privileged to other blood products. Correction of coagulation disorders and thrombocytopenia is unnecessary in most cases, and excessive transfusions of fresh frozen plasma and platelets can exacerbate portal blood volume, which is a risk factor for hemorrhage. Octreotide (50 mcg IV bolus followed by 50 mcg/h IV infusion) should be started. Prophylactic parenteral antibiotics are associated with a decreased risk of rebleeding and should be given. Diagnostic paracentesis should also be done if ascites is present.

TABLE 51.2 Management of Acute Variceal Bleeding

Management of Acute Variceal Bleeding
Resuscitate hypovolemic shock
Assessment of airway and intubation if airway protection necessary
Octreotide 50 mcv IV bolus followed by 50 mcg/h IV infusion
Blood and urine culture; diagnostic paracentesis if large-volume ascites present
Prophylactic parenteral antibiotics
Upper endoscopy
TIPS, BRTO, and Blakemore tube as needed for variceal bleeding refractory to endoscopic management

BRTO, balloon-occluded retrograde transvenous obliteration; IV, intravenous; TIPS, transjugular intrahepatic shunt.

Upper endoscopy should be performed promptly as both band ligation and sclerotherapy can result in effective hemostasis for esophageal varices. TIPS is an option for variceal bleeding refractory

to endoscopy and for bleeding gastric varices. Early TIPS placement (within 24-48 hours of endoscopy) in Child class B cirrhosis with visible bleeding at endoscopy, or Child class C cirrhosis, has been advocated as a strategy that reduces the risk of rebleeding and prolongs survival based on randomized trials.

Balloon-occluded retrograde transvenous obliteration (BRTO) is another therapy that may be effective in the management of bleeding from gastric or ectopic varices. Balloon tamponade devices (Blakemore tube) can also be inserted temporarily in cases where either endoscopy or TIPS is delayed or unsuccessful. Noncardioselective beta-blockers (propranolol, nadolol, or carvedilol) are effective at reducing the risk of initial and recurrent variceal bleeding; however, they should be introduced only after acute bleeding is controlled and hemodynamics are stable.

Transjugular Intrahepatic Portosystemic Shunt

TIPS is a channel created between the hepatic vein and the intrahepatic portion of the portal vein. It is placed to reduce the portal pressure in patients with complications related to portal hypertension, most commonly variceal hemorrhage or ascites. Contraindications to TIPS include pulmonary hypertension, heart failure, severe encephalopathy, polycystic liver disease, tumor in the path of the TIPS, and unrecanalizable portal vein thrombosis.

Acute-on-Chronic Liver Failure

An acute deterioration of liver function in patients with cirrhosis that results in the failure of one or more extrahepatic organs has been used to describe the category of ACLF. This is distinct from acute liver failure and decompensated cirrhosis. Precipitants of ACLF include alcohol consumption, infection, and reactivation of hepatitis B infection. The cause is undiagnosed in as many as 45% of cases. The mortality risk increases with an increase in organ failure; for

example, in the setting of the failure of three or more organs, the 28-day transplant-free mortality risk was 78%.

Malnutrition

It is estimated that almost two-thirds of patients with end-stage liver disease awaiting liver transplant are malnourished. Patients admitted to the ICU are frequently made nil per os (NPO) for a variety of reasons, including gastrointestinal bleeding, high vasopressor requirements, procedure planning, and encephalopathy. In patients whose oral intake is insufficient to meet their nutritional needs, enteral nutrition should be initiated within 24 to 48 hours of ICU admission and any barriers to nutritional administration should be addressed. Although there is limited data on the energy targets in patients with cirrhosis in the ICU, higher protein goals are generally recommended, with a target of 1.2 to 2 g/kg/d, based on ideal body weight. Parenteral nutrition can be considered in hospitalized patients that meet criteria for frailty or sarcopenia. This is preferable to no nutritional supplementation but should be considered as a second-line option to enteral nutrition.

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SECTION XIII Gastrointestinal Disorders

52 Gastrointestinal Bleeding

Surachai Amornsawadwattana and C. Prakash Gyawali

Gastrointestinal bleeding (GIB) is a common medical emergency that frequently results in emergency department evaluations and intensive care unit (ICU) admissions. There were estimated 530,855 admissions in 2018 and 9,548 deaths in 2019 in the United States, with nearly $302 million spent for the care of patients with GIB. The estimated mortality rate from upper GI bleeding (UGIB) has been largely stable at 6% to 12%, whereas the mortality rate from lower GI bleeding (LGIB) remains low (<5%).

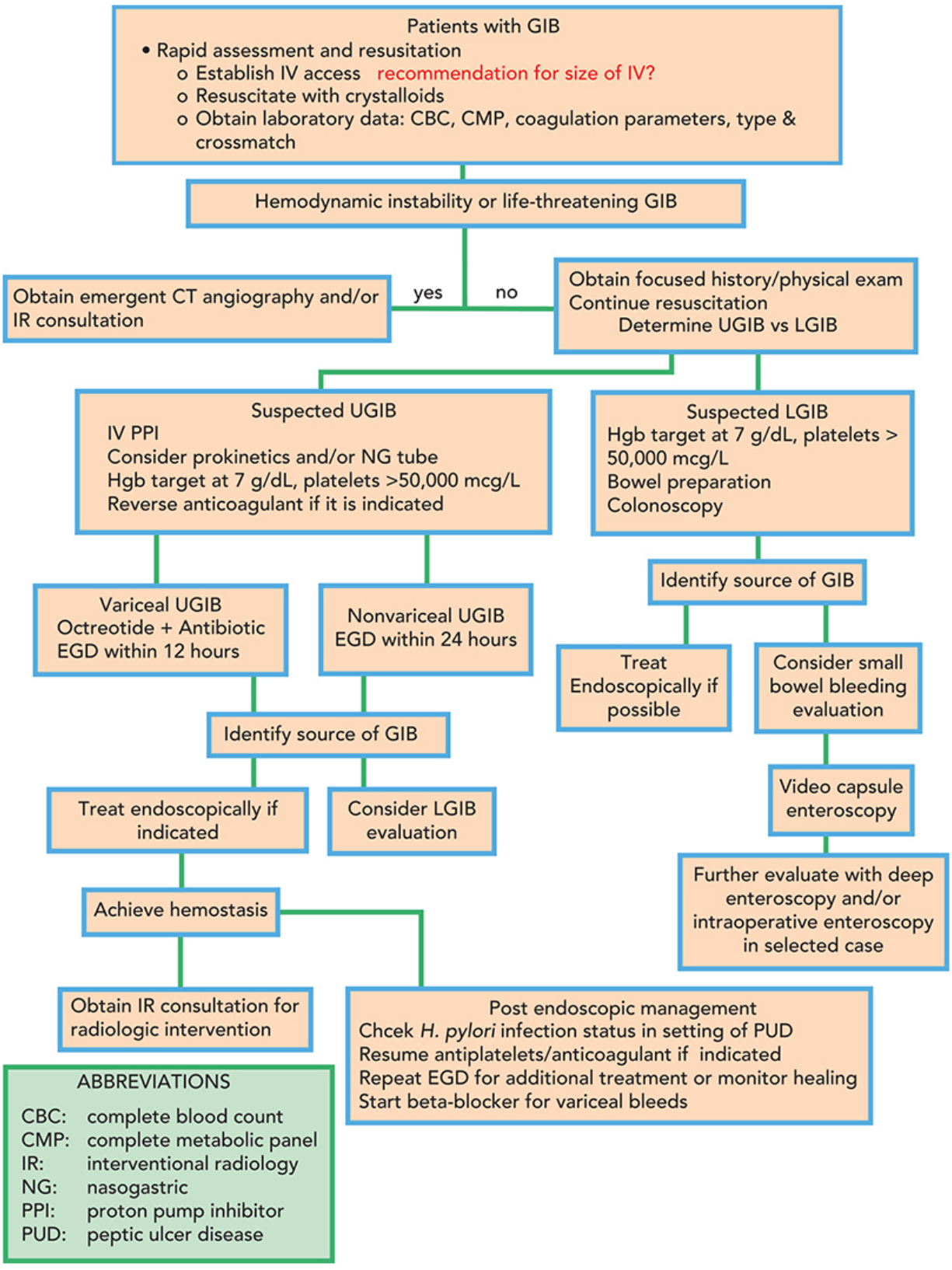
Traditionally, GIB was categorized into UGIB and LGIB based on whether bleeding was localized proximal or distal to the ligament of Treitz. With modern endoscopic evaluation and radiographic diagnostic options, bleeding from the small bowel can be accurately localized; hence, GIB is now categorized as UGIB (bleeding proximal to the duodenal ampulla of Vater), small bowel bleeding (bleeding between the ampulla of Vater and the ileocecal valve), and LGIB (bleeding distal to the ileocecal valve). The majority of UGIB is nonvariceal (80%-90%), angioectasia-related bleeding dominates in the small bowel, whereas diverticular hemorrhage is the most common cause of LGIB. Lately, the incidence of nonvariceal UGIB has declined in all populations, possibly because of lower *Helicobacter pylori* incidence and widespread use of proton pump inhibitors (PPIs).

Resuscitation and Early Management

Initial resuscitation and early management of acute GIB do not vary by location. One of the first assessments in acute GIB is determining the severity of blood loss (Algorithm 52.1). If a previously

normotensive or hypertensive patient develops resting hypotension, as much as 20% to 25% of the circulating volume may have been lost, and bleeding is considered massive. In the absence of resting hypotension, postural or orthostatic hypotension (a drop of systolic blood pressure of 15 mm Hg or an increase in heart rate of 20 beats per minute) indicates loss of 10% to 20% of the circulating volume. Bleeding is considered minor if neither of these conditions are met, indicating a loss of less than 10% of circulating volume. In all instances, two large-bore intravenous (IV) lines or a central line are urgently placed, and crystalloids are administered IV. Routine use of colloids is not recommended. Rapid repletion of circulating volume is crucial when blood loss approaches massive, and transfusion of packed red blood cells (RBCs) needs to be arranged. Therefore, blood is drawn for blood count, metabolic profile, coagulation parameters, blood typing, and cross-matching. If available, thromboelastography or thromboelastometry can be used to better assess platelet function and coagulopathy. When type-specific blood is not immediately available, O-negative blood may need to be transfused, using rapid infusing devices if necessary. A restrictive blood transfusion strategy with a hemoglobin target of 7 g/dL is recommended; higher hemoglobin values may ultimately be necessary in patients with clinical evidence of intravascular volume depletion or comorbidities, such as coronary artery disease. Generally, platelets should be transfused when a platelet count drops below 50,000 /mcL. Oxygen is administered by nasal cannula to improve oxygen-carrying capacity of blood, and vital signs and urine output are constantly monitored.

ALGORITHM 52.1 Management of Patients With Gastrointestinal Bleeding


Patients with GIB
• Rapid assessment and resusitation
o Establish IV access recommendation for size of IV?
o Resuscitate with crystalloids
o Obtain laboratory data: CBC, CMP, coagulation parameters, type & crossmatch
Hemodynamic instability or life-threatening GIB
yes
no
Obtain emergent CT angiography and/or IR consultation
Obtain focused history/physical exam
Continue resuscitation
Determine UGIB vs LGIB
Suspected UGIB
IV PPI
Consider prokinetics and/or NG tube
Hgb target at 7 g/dL, platelets >50,000 mcg/L
Reverse anticoagulant if it is indicated
Suspected LGIB
Hgb target at 7 g/dL, platelets > 50,000 mcg/L
Bowel preparation
Colonoscopy
Variceal UGIB
Octreotide + Antibiotic
EGD within 12 hours
Nonvariceal UGIB
EGD within 24 hours
Identify source of GIB
Treat Endoscopically if possible
Consider small bowel bleeding evaluation
Identify source of GIB
Video capsule enteroscopy
Treat endoscopically if indicated
Consider LGIB evaluation
Further evaluate with deep enteroscopy and/or intraoperative enteroscopy in selected case
Achieve hemostasis
Obtain IR consultation for radiologic intervention
Post endoscopic management
Chcek H. pylori infection status in setting of PUD
Resume antiplatelets/anticoagulant if indicated
Repeat EGD for additional treatment or monitor healing
Start beta-blocker for variceal bleeds
ABBREVIATIONS
CBC: complete blood count
CMP: complete metabolic panel
IR: interventional radiology
NG: nasogastric
PPI: proton pump inhibitor
PUD: peptic ulcer disease

Once the patient has been hemodynamically stabilized, further evaluation can resume. Pertinent history includes presentation of GIB, comorbidities (cardiac, renal, pulmonary, peptic ulcer diseases, inflammatory bowel disease [IBD], cancer), current medications (nonsteroidal anti-inflammatory drugs [NSAIDs], antiplatelet agents, anticoagulants), history of GI surgeries, alcohol use, and concurrent GI symptoms. Physical examination should focus on hemodynamics, signs of chronic liver disease, abdominal examination, and digital rectal examination. Presentation may help localize the potential site and source of GIB. Hematemesis or coffee-ground emesis establishes UGIB as the source. Melena typically indicates a proximal gut source, but can develop from bleeding sites as far distal as the small intestine or even the colon. Hematochezia or bright red blood in the stool usually suggests LGIB, but an upper GI source may be present in approximately 10% with hematochezia and altered hemodynamic parameters.

Aspiration of bloody gastric content through a nasogastric (NG) tube establishes UGIB, potentially of poor prognosis without intervention, but lack of bloody aspirate does not exclude an UGIB source. Although NG lavage may help predict high-risk lesions, it does not appear to impact clinical outcome, and maintenance of NG tube only needs consideration in selected patients. Early indicators for ICU care include massive bleeding, hemodynamic compromise, variceal bleeding, bleeding onset while hospitalized for an unrelated illness, and other factors that predict a poor outcome (Table 52.1). Hemoccult testing of NG aspirates and stool has very little value in the assessment of GIB and should not be performed.

TABLE 52.1 Factors Predicting Poor Outcome After Acute Upper Gastrointestinal Bleeding

Age >65 y
Comorbid medical illnesses (liver disease, COPD, renal failure, coronary artery disease, malignancy)
Variceal bleeding
Systolic blood pressure <100 mm Hg at presentation

Large peptic ulcers >3 cm
Active bleeding (spurting blood vessel) at endoscopy
Multiple units of blood transfusion
Onset of acute bleeding when hospitalized for unrelated illness
Need for emergency surgery to control bleeding

COPD, chronic obstructive pulmonary disease.

Coagulopathy from vitamin K antagonists may need reversal when GIB is clinically significant. Fresh frozen plasma (FFP) can be considered in rare instances when GIB is life threatening, especially when the international normalized ratio (INR) exceeds therapeutic range, or when massive transfusion is undesirable and prothrombin complex concentrate (PCC) is not available. Vitamin K administration is not advisable in acute GIB as this does not have an immediate effect, but may have a role if anticoagulation is being permanently discontinued, or if slow correction of a supratherapeutic INR is needed. PCC use should be reserved for supratherapeutic INR, life-threatening GIB, or when massive transfusion needs to be avoided. Overall, if a supratherapeutic INR needs correction, PCC is favored over FFP because of more reliable correction with rapid onset of action.

Direct oral anticoagulants (DOACs) are being increasingly utilized for fast onset, ease of use, and possible decreased GIB risk compared to vitamin K antagonists. Reversing agents for DOAC, though available, are not used routinely in GIB due to high cost and limited evidence of benefit. Nevertheless, these agents and PCC are options in life-threatening GIB from DOAC use within 24 hours of GIB. Platelet transfusion is not recommended for patients on antiplatelet agents presenting with GIB. Interruption of aspirin is not necessary when patients on aspirin for secondary cardiovascular prevention present with GIB, but if held, aspirin can be resumed within 24 hours after endoscopic hemostasis is achieved. There is no role for tranexamic acid use in GIB. Any decision of anticoagulant reversal needs direct input from cardiologists, hematologists, or other providers involved in each patient’s anticoagulant management.

Upper Gastrointestinal Bleeding

Acute UGIB can be variceal or nonvariceal (Table 52.2), each requiring differing investigation and management strategies, with varied short- and long-term morbidity and mortality. Therefore, early clinical evaluation of acute UGIB seeks to determine whether bleeding is variceal or nonvariceal, with the understanding that this assessment may not always be accurate or even possible.

TABLE 52.2 Etiology of Upper Gastrointestinal Bleeding

Peptic ulcer disease (accounts for ~50%)
Gastric ulcers
Duodenal ulcers
Gastric erosions and gastritis
Esophageal and gastric varices (accounts for 10%-20%)
Stress ulcers
Mallory-Weiss tear
Esophagitis and esophageal ulcers
Vascular abnormalities (angiodysplasia, Dieulafoy lesion, telangiectasia)
Portal hypertensive gastropathy
Neoplasms, benign and malignant
Hemobilia (bleeding into bile ducts)
Hemosuccus (bleeding into pancreatic ducts)
Aortoenteric fistula

Initial management of acute UGIB is pharmacologic. Octreotide, a somatostatin analogue, lowers splanchnic and portal venous pressure in the short term, with slowing or cessation of variceal UGIB. Early administration of octreotide is recommended when acute variceal UGIB is suspected (50 mcg IV bolus, followed by 50 mcg/h continuous infusion for a total duration of 2-5 days). In addition, antibiotic prophylaxis (IV ceftriaxone 1 g/d for 7 days) is administered to prevent infectious complications in variceal bleeding, particularly spontaneous bacterial peritonitis.

In all other instances, PPIs are administered to suppress gastric acid (as clot formation and stabilization are facilitated in an alkaline milieu) and to downstage endoscopic bleeding lesions, which may decrease the need for endoscopic therapy. IV bolus administration (omeprazole, 40 mg every 12 hours IV or equivalent) is effective for this purpose; however, IV bolus followed by infusion (pantoprazole 80 mg, then 8 mg/h or equivalent) has been advocated for rapid ongoing bleeding. Stable patients without active ongoing bleeding can tolerate oral PPI administration, and double dose (omeprazole, 40 mg or equivalent) 2 times daily may be beneficial at least until endoscopy is performed. In patients who do not undergo endoscopy, double-dose PPI administered twice daily reduces the likelihood of rebleeding or the need for surgery in acute peptic ulcer bleeding.

A crucial adjunct to pharmacologic therapy is endoscopy, both for definitive diagnosis of the bleeding lesion and for delivery of endoscopic hemostatic interventions that lower the risks for rebleeding, other morbidity including surgery, and mortality. Timing of endoscopy depends on the degree of bleeding, whether bleeding is ongoing, possible etiology of UGIB (nonvariceal vs variceal), and the patient's overall condition (Table 52.3). In general, an upper endoscopy should be performed within 12 and 24 hours in patients with suspected variceal and nonvariceal UGIB, respectively. Urgent endoscopy is generally indicated in any patients with significant or ongoing bleeding. Hemodynamic parameters should be in the process of being normalized when endoscopy is performed. Administration of prokinetic agents such as metoclopramide (5-10 mg IV) or erythromycin (250 mg IV) induces gastric emptying to allow a cleaner endoscopic field, thus reducing the need for repeat endoscopy. Lavage using large-bore, double-lumen orogastric tubes can clear the stomach of blood and clots. In some instances, especially if large volumes of luminal blood or massive intraluminal clots are encountered, endoscopy may need to be repeated later. However, a routine second-look endoscopy is not recommended. Endotracheal intubation should be considered in patients with massive UGIB or patients with altered mental status to protect the airway for safe endoscopy. Conventional endoscopic hemostatic

approaches include variceal band ligation, sclerotherapy, and glue injection for variceal UGIB and epinephrine injection, thermal cautery, hemoclip deployment, and sclerosant injection for nonvariceal UGIB. Placement of a Sengstaken-Blakemore or similar tube can tamponade varices and temporarily stabilize variceal GIB (Table 52.4). Over-the-scope clips, coagrasper hemostatic forceps, hemostatic powder, endoscopic suturing, mucosal ablation devices, and esophageal stents are newer devices and approaches that can be used to treat or stabilize GIB lesions.

TABLE 52.3 Triage of Patients With Acute Upper Gastrointestinal Bleeding

Admission to intensive care unit
- Hypotension at presentation
- Moderate-to-severe bleeding onset while admitted for an unrelated illness
- Ongoing hemodynamic instability despite resuscitation
- Absence of adequate hematocrit increase despite blood transfusion
- Low initial blood count (hematocrit <25% with cardiopulmonary disease or stroke, <20% otherwise)
- Bright or dark red NG tube aspirate, especially if it does not clear with lavage
- Prolonged coagulation parameters (prothrombin time >1.2 times the control value)
- Myocardial infarction, stroke, or other systemic complications of rapid blood loss
- Any unstable comorbid disease, including altered mental status
- Variceal bleeding
- Evidence of active oozing, spurting, or visible vessel on endoscopy

Admission to regular hospital floor
- Stable hemodynamic parameters after initial resuscitation
- Mild hematocrit drop <5% from baseline and/or baseline hematocrit .30%
- Stable coagulation parameters
- Coffee grounds on NG tube aspirate that clears with lavage
- No systemic complications from blood loss
- No bleeding source found on upper endoscopy
- Nonvariceal bleeding source without active bleeding; bleeding lesion with a clean base or pigmented base

Emergent or urgent upper endoscopy
- Suspected or known variceal bleeding

Hemodynamic instability despite resuscitation
Bright red or dark red NG aspirate, especially if it does not clear with lavage
Absence of appropriate hematocrit increase despite blood transfusion

NG, nasogastric.

TABLE 52.4 Balloon Tamponade for Variceal Bleeding

Indications

Temporary control of variceal bleeding (gastric, esophageal, or both)
Access to endoscopic or radiologic therapy not immediately available
To stabilize patient for transport
Efficacy is thought to be better when combined with pharmacologic therapy.

Equipment

Sengstaken-Blakemore tube (three lumen), Minnesota tube (four lumen), Linton-Nachlas tube (gastric balloon alone), or similar tube
Nasogastric tube when three-lumen tube or gastric balloon alone is used.
Soft restraints
Traction mechanism (typically a football helmet, weights, or orthopedic traction system)
Manometer
Tube clamps, surgical scissors
Topical anesthetic, tube connectors, syringes

Technique

Patient needs to be intubated and sedated, with soft restraints in place.
Test balloons, check intraluminal pressures at full inflation using manometer.
Gastric lavage until clear through nasogastric tube, which is then removed.
Introduce lubricated tube through mouth.
When gastric juice or blood is aspirated through gastric lumen, check tube position radiographically.
With manometer attached to measuring port, fill gastric lumen with air in 100-mL increments to recommended volume for a particular tube (typically 450-500 mL).
If rapid pressure increase noted on manometer, tube may have been inflated in esophagus; deflate immediately, advance tube, reinflate.
Clamp air inlet for gastric balloon, pull back, secure to traction device.
If esophageal balloon inflation is desired, inflate esophageal balloon to 30-45 mm Hg pressure as measured by manometer on measuring port.
Further traction can be applied if bright red blood continues to be aspirated through gastric port.
With three-lumen tubes, place nasogastric tube so that tip is 3-4 cm above esophageal balloon, connect to intermittent suction.

Deflate balloons for 5 min every 5-6 h to reduce the risk of pressure necrosis.
Keep balloons inflated for up to 24 h as needed.
Efficacy ~80% when correctly placed.

Complications

Complications occur in 15%-30%; mortality rate is around 6%.
Major complications include asphyxia, airway occlusion, esophageal rupture, esophageal and gastric pressure necrosis.
Aspiration pneumonia, epistaxis, pharyngeal erosions

Short- and long-term outcomes of therapy depend on the bleeding lesion. Rebleeding rates are as high as 30% to 40% with variceal bleeding and around 15% to 20% in nonvariceal bleeding. Rebleeding rates are stratified by the presence or absence of stigmata of recent hemorrhage in peptic ulcer bleeding (Table 52.5). When rebleeding occurs, repeat endoscopic therapy can be considered, with adjunctive interventional radiology consultation in patients who fail endoscopic therapy or when high-risk stigmata suggest likely failure of endoscopic hemostasis. Variceal GIB can be managed by the placement of a transjugular intrahepatic portosystemic shunt (TIPS). Gastric varices related to portal hypertension are managed with TIPS or balloon-occluded retrograde transvenous occlusion (BRTO), while gastric varices from splenic vein thrombosis may require splenectomy for successful management. Endoscopic ultrasound-guided embolization can be considered in select patients with bleeding gastric varices.

TABLE 52.5 Outcome After Endoscopic Therapy of Peptic Ulcers

Endoscopic Finding	Risk for Rebleeding (%) (After Treatment)	Mortality (%) (After Treatment)
Clean ulcer base	<5	2

Endoscopic Finding	Risk for Rebleeding (%) (After Treatment)	Mortality (%) (After Treatment)
Flat pigmented spot	10 (<1)	3 (<1)
Adherent clot	22 (5)	7 (<3)
Visible vessel	43 (15)	11 (<5)
Active bleeding	55 (20)	11 (<5)

Data from Laine L, Petersen WL. Bleeding peptic ulcer. *N Engl J Med*. 1994;331:717-727.

Patients with high-risk peptic ulcers requiring endoscopic hemostasis should be observed in the hospital for at least 72 hours. Testing for *H. pylori* infection in all patients with peptic ulcers will allow eradication when positive, which reduces the risk for recurrent bleeding.

Lower Gastrointestinal Bleeding

The incidence of acute LGIB in the literature ranges anywhere from 33 to 87 out of 100,000 population and appears to be on the rise relative to UGIB. In contrast to UGIB, acute LGIB is associated with less hemodynamic compromise, lower transfusion requirement, and lower 1-year mortality (4.2%). Typically, acute LGIB is self-limiting, but bleeding can be severe depending on the etiology, and recurrence rates are higher than that for UGIB (46% at 5 years). Similar to acute UGIB, patients who develop acute LGIB while hospitalized for any indication have a worse outcome, with an estimated mortality of 23% during admission. In recent years, advances in colonoscopic and radiologic therapies in actively bleeding patients (such as hemoclip use, superselective embolization of the bleeding vessel) have reduced the need for emergent surgery.

Diverticular bleeding is the most common cause of LGIB. Bleeding is arterial, resulting in clinically significant painless episodes of bright red blood in the stool. Diverticular bleeding spontaneously ceases in more than 80% of patients, but one quarter may develop recurrent bleeding. Other common etiologies of LGIB include colonic ischemia, hemorrhoids, angioectasia, malignancy, postpolypectomy bleeding, colitis, NSAID-induced ulcer, stercoral colitis, and radiation proctopathy (Table 52.6). Less common causes are colonic/rectal varices and Dieulafoy lesion. It is not unusual for no source to be identified, although this partly depends on the timing of colonoscopy.

TABLE 52.6 Causes of Acute Lower Gastrointestinal Bleeding

Diverticulosis
Angiodysplasia
Neoplasia: includes large polyps and cancers
Postpolypectomy bleeding
Colitis: includes inflammatory and infectious causes
Ischemia
Anorectal causes: hemorrhoids, anal fissure
Radiation proctopathy and colopathy
Aortoenteric fistula (rare)
Dieulafoy lesion (rare)
Rectal varices (rare)

Certain clinical and laboratory features at presentation may identify patients at risk for higher short-term morbidity, including recurrent bleeding, hemodynamic compromise, syncope, aspirin or anticoagulant use, more than two comorbid medical conditions, and continued bleeding 4 hours after initial presentation. Others have identified prolongation of prothrombin time greater than 1.2 times the control value and altered mental status as additional predictors of poor outcome. These characteristics are useful in making triage decisions, especially in identifying patients who could benefit from

admission to an ICU and patients who need urgent investigative procedures (Table 52.7).

TABLE 52.7 Triage of Patients With Acute Lower Gastrointestinal Bleeding

Admission to intensive care unit
Hypotension (systolic blood pressure <115 mm Hg) at presentation
Moderate-to-severe bleeding onset while admitted for an unrelated illness
Ongoing hemodynamic instability despite resuscitation
Absence of adequate hematocrit increase despite blood transfusion
Low initial blood count (hematocrit <25% with cardiopulmonary disease or stroke, <20% otherwise)
Prolonged coagulation parameters (prothrombin time 1.2 times the control value or more)
Myocardial infarction, stroke, or other systemic complications of rapid blood loss
Any unstable comorbid disease, including altered mental status
Ongoing significant bleeding 4 h after presentation
Evidence of active oozing, spurting, or visible vessel on endoscopy
Requirement of angiography for localization or control of bleeding
Admission to regular hospital floor
Stable hemodynamic parameters after initial resuscitation
Mild hematocrit drop (<5% from baseline and/or baseline hematocrit >30%)
Stable coagulation parameters
No systemic complications from blood loss
Absence of ongoing bleeding 4 h after presentation
Emergent *upper* endoscopy in patients with bloody stool
Bright red or dark red blood in stool with hemodynamic compromise
Bloody NG aspirate
Suspicion of aortoenteric fistula (distal duodenum needs evaluation)

NG, nasogastric.

All patients presenting with acute hematochezia eventually need a full colonoscopy with terminal ileal intubation for diagnosis of the bleeding source. However, colonoscopy may not need to be performed in those with limited or significantly improved LGIB and a high-quality colonoscopy identifying colonic diverticulosis within the previous 12 months. Colonoscopy can be performed on a nonemergent basis as there is no evidence to support the benefit of

urgent colonoscopy within 24 hours to improve clinical outcomes. Unprepped colonoscopy or flexible sigmoidoscopy is not recommended, except in specific instances where bleeding is from a likely distal colonic source. If the culprit lesion is identified, several endoscopic options are available for hemostasis.

When early colonoscopy is precluded due to rapid bleeding, hemodynamic instability, significantly impaired coagulation parameters, comorbid illnesses, or inability to tolerate a bowel preparation, a multidetector computerized tomography with angiography (CTA) is a fast and convenient means to localize bleeding. A tagged RBC scan can also be useful, picking up bleeding rates as low as 0.1 to 0.5 mL/min in research settings, although only 45% of tagged RBC scans demonstrate extravasation in the clinical setting. Rapidly positive scans have the highest accuracy and predict the best likelihood of identification of the bleeding site at subsequent angiography. Delayed positive scans have a much lower sensitivity in accurately localizing the bleeding source, as intestinal peristalsis may impact the reading.

For patients with positive imaging findings for a bleeding source or for those too unstable for localizing studies, selective angiography represents the final option in acute LGIB other than surgery. If a rapidly bleeding site is identified on angiography, vasopressin can be infused after selective catheterization of the bleeding vessel. This may induce vasoconstriction and cessation of bleeding. Alternatively, embolization of the bleeding vessel can be attempted. Complications of angiography can be dye related (renal failure), procedure related (hematoma formation, retroperitoneal bleeding, intestinal ischemia), or a result of vasopressin infusion (arrhythmias, myocardial infarction).

One of the dilemmas in patients with acute LGIB is a clinical determination of whether the lesion identified on diagnostic testing is indeed the source for the patient’s bleeding episode. This is particularly important as active bleeding or stigmata of recent bleeding are not always identified on potential bleeding lesions. At times, more than one potential bleeding lesion may be identified. Criteria have been suggested to assess the level of diagnostic

certainty in interpreting diagnostic tests in acute LGIB, which may help determine the nature of definitive management or follow-up needed, especially when surgery is recommended based on the results of diagnostic tests (Table 52.8).

TABLE 52.8 Levels of Diagnostic Certainty in Interpreting Test for Acute Lower Gastrointestinal Bleeding

Definitive evidence of a bleeding source
Active oozing or bleeding visualized at colonoscopy or angiography
Stigmata of recent bleeding (adherent clot, nonbleeding visible vessel) identified on colonoscopy
Positive tagged RBC scan associated with either of the above mentioned
Circumstantial evidence of a bleeding source
Single potential bleeding source on colonoscopy with fresh blood in the same segment
Single potential bleeding source on colonoscopy or angiography in the same area as a positive tagged RBC scan
Bright or dark red blood on objective stool testing, single potential source (without endoscopic stigmata) on colonoscopy, negative upper endoscopy and capsule endoscopy
Equivocal evidence of a bleeding source
"Hematochezia" unconfirmed by objective testing, potential sources (without endoscopic stigmata) on colonoscopy or capsule endoscopy

RBC, red blood cell.

Small Bowel Bleeding

Small bowel bleeding accounts for 5% to 10% of patients presenting with GIB. The etiology of small bowel bleeding is dependent on the patient's age. In general, angiodysplasias are the most common mechanism of small bowel bleeding. Other etiologies include tumors, small bowel injury from NSAIDs, radiation enteropathy, bleeding diverticulum, Crohn's disease, aortoenteric fistula, varices, and Dieulafoy lesion (Table 52.9). Video capsule endoscopy (VCE), with a diagnostic yield of 38% to 83%, is considered the test of choice in

evaluating stable patients with suspected small bowel bleeding following negative upper and lower endoscopy. The drawbacks of VCE include a lack of readily available real-time interpretation, accurate localization of findings is almost impossible, and no therapeutics can be administered. False-negative and false-positive results can occur. Deep enteroscopy (balloon-assisted enteroscopy and spiral enteroscopy) allows the reach of almost the entire small bowel and can provide endoscopic therapy, but may be associated with a higher degree of morbidity and complications compared with routine endoscopic procedures. Typically, deep enteroscopy is directed by VCE localization of a bleeding source, but can be considered as a first-line approach in patients with high suspicion of small bowel bleeding, altered anatomy, or when VCE is contraindicated. In hemodynamically unstable patients with suspected small bowel bleeding, radiologic evaluation (CTA and/or angiography) should be performed instead of VCE. Infrequently, surgical management, either for surgical resection or for intraoperative enteroscopy, may be required in treating actively bleeding sources identified in the small bowel (Table 52.10).

TABLE 52.9 Causes of Small Bowel Gastrointestinal Bleeding

Angiodysplasia
Neoplasia: includes cancers, stromal tumors, lymphoma
Enteritis: includes inflammatory and infectious causes
Radiation enteritis and enteropathy
Meckel diverticulum
Aortoenteric fistula (rare)

TABLE 52.10 Suspected Small Bowel Bleeding

Approach
If bleeding is rapid and severe with hemodynamic compromise, consider immediate selective angiography and embolization of bleeding site.

If bleeding is rapid but patient can be stabilized, perform CT angiography or tagged RBC scan.
If bleeding is not rapid and patient is stable, or initial radiographic studies show no active bleeding, perform upper and lower endoscopy and consider second-look upper endoscopy in cases of recurrent melena.
If small bowel bleeding is suspected at presentation, consider push enteroscopy as the initial choice for upper endoscopy.
After nondiagnostic upper and lower endoscopy, perform video capsule endoscopy.
Consider CT or MR enterography in cases of suspected bowel obstruction or negative capsule endoscopy to look for luminal or mural small bowel lesions.
If capsule endoscopy or radiographic studies confirm small bowel bleeding, perform deep enteroscopy (balloon-assisted enteroscopy or spiral enteroscopy) to treat lesions.
Consider retrograde balloon enteroscopy in instances of ileal bleeding.
Consider intraoperative enteroscopy:
Healthy individuals with significant bleeding recurrences and a potential small bowel source
For small bowel bleeding after ineffective repeated attempts at endoscopic treatment
For localization of a likely small bowel source, for surgical resection
Provocative measures (administration of heparin, thrombolytic agents, or vasodilators) are very rarely used and should not be recommended, except in very refractory situations, in patients without comorbidities, under very close observation by experienced personnel.

Small bowel bleeding, formerly obscure gastrointestinal bleeding, consists of persistent or recurrent bleeding, with no bleeding source evident on conventional upper and lower endoscopy.
CT, computed tomography; MR, magnetic resonance; RBC, red blood cell.

Surgical treatment of GIB has become infrequent in the present day. However, surgery continues to have a role in treating patients with bleeding peptic ulcer refractory to endoscopic and angiographic therapy, bleeding cancer, certain types of anorectal bleeding, aortoenteric fistula bleeding, or patients with concomitant other surgical indications (peritonitis, gangrene, obstruction, etc). The timing of surgical consultation is physician and institution dependent.

SUGGESTED READINGS

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53 Acute Pancreatitis

Gabriel D. Lang

Acute pancreatitis is the most common reason for gastrointestinal inpatient admission in the United States and is associated with significant morbidity, mortality, and cost. This disease affects over 1.5 million people annually worldwide. The incidence of acute pancreatitis is rising, and mortality rates of 5% to 20% have been reported. There are a variety of causes of acute pancreatitis, but gallstones and alcohol account for nearly 70% (Table 53.1). Acute pancreatitis is inflammation of the pancreas associated with varying degrees of auto-digestion, edema, necrosis, and hemorrhage of pancreatic tissue. Acute pancreatitis can be associated with a systemic inflammatory response that can impair the function of other organs and evolve into persistent organ failure. The clinical course varies from mild, self-limited episodes to severe pancreatitis with associated multiorgan dysfunction, local complications such as infected peripancreatic fluid collections, or extra-pancreatic complications such as venous thrombosis. Up to 20% of patients presenting with pancreatitis have a severe course, often requiring critical care. The mortality rate of severe pancreatitis with infectious complications is 10% to 20% and can increase to over 50% in the presence of persistent organ failure.

TABLE 53.1 Causes of Acute Pancreatitis

Common	Uncommon	Rare
Gallstones Alcohol	Pancreas divisum	Malignancy
	Autoimmune pancreatitis	Hereditary

Common	Uncommon	Rare
	Hypertriglyceridemia	Vascular (eg, ischemia)
	Medications	Abdominal trauma
	Iatrogenic (post-ERCP)	Toxins (eg, scorpion bite)
	Sphincter of Oddi dysfunction	Hypercalcemia
	Idiopathic	Infection (eg, mumps, coxsackie)

ERCP, endoscopic retrograde cholangiopancreatography.

Evaluation

The diagnosis of acute pancreatitis should be suspected in patients with acute onset of severe epigastric pain with tenderness upon palpation. To confirm acute pancreatitis, two of the following three criteria are required: (1) acute onset of severe epigastric pain, which may radiate to the back; (2) elevation in serum amylase or lipase levels exceeding 3 times the upper limit of normal; and (3) characteristic findings of pancreatic inflammation on imaging. Indications for monitored or intensive care are described in Table 53.2. The evaluation of a patient with suspected acute pancreatitis should begin with a careful history, with attention to symptom onset, alcohol use, gallstone disease, prior pancreatitis, review of medications, and family history of pancreatitis. The principal symptom on history is abdominal pain, typically in the epigastric region, which can radiate to the back. It typically presents acutely and can be associated with nausea and vomiting. On physical examination, palpation demonstrates severe abdominal tenderness and guarding. Inactive bowel sounds may be indicative of ileus. In severe cases, signs of systemic inflammatory response syndrome (SIRS), with fever, tachycardia, and tachypnea, may be

present. Additional findings suggesting severe disease include diminished breath sounds, hypoxia, and altered mental status. Cullen sign (periumbilical ecchymosis) and Grey Turner sign (flank ecchymosis) are rare findings and indicate hemorrhagic pancreatitis in the setting of pancreatic necrosis. Early in the course of pancreatitis, digestive enzymes leak out of pancreatic acinar cells and enter the systemic circulation. Serum lipase levels rise earlier and remain elevated longer than serum amylase levels. Elevated serum lipase levels, exceeding 3 times the upper limit of normal, are more sensitive markers than serum amylase for the diagnosis of acute pancreatitis (82%-100% vs 67%-83%). However, it should be noted that enzyme levels may be within normal limits in 5% of patients at the time of hospital admission. Additional laboratory investigations required at the onset of suspected acute pancreatitis to aid in risk stratification include liver function tests, complete blood count (CBC), blood urea nitrogen (BUN), calcium, and creatinine. Elevations in liver enzymes (particularly transaminases) with or without associated hyperbilirubinemia suggest the presence of bile duct stones or compression of the common bile duct by edema. Imaging studies may be needed when there is doubt in the diagnosis or for documentation of the severity of illness. It is important to note that in patients with characteristic abdominal pain and elevation in serum amylase/lipase, imaging is not necessary to establish the diagnosis of acute pancreatitis. An abdominal ultrasound should be performed to assess for cholelithiasis or choledocholithiasis, especially in cases of suspected gallstone pancreatitis. Early detection of gallstones helps dictate further management either by endoscopic retrograde cholangiopancreatography (ERCP) or cholecystectomy. Cross-sectional imaging is not a mandatory part of the initial evaluation but can be performed if there is concern for complications of acute pancreatitis. Contrast-enhanced computed tomography (CECT) is the best modality for evaluating pancreatic inflammation, necrosis, and peripancreatic fluid collections. The most common findings on imaging in uncomplicated interstitial pancreatitis are enlargement of all or part of the pancreas with blurring of the margins and inflammatory changes. CECT done at the initial

presentation may underestimate disease severity since it can take up to 72 hours for necrosis to develop. Therefore, CECT should be delayed unless there is a concern for other complications or if the diagnosis is in doubt. For recurrent acute pancreatitis (two or more episodes), a detailed workup is warranted, including immunoglobulin G4 (IgG4) levels to check for autoimmune pancreatitis, triglycerides, and serum calcium levels. Medications should be thoroughly reviewed, as iatrogenic causes account for 2% of pancreatitis. Endoscopic ultrasound can be performed to assess for pancreatic cancer in patients who do not have an identified etiology. Further workup may include a genetic workup, evaluation for pancreas divisum, and an infectious workup. Empiric cholecystectomy should be considered in patients with no identifiable cause for recurrent acute pancreatitis, even if liver function tests and gallbladder imaging are normal. No clear etiology of pancreatitis will be found in 10% to 20% of patients (idiopathic pancreatitis).

TABLE 53.2 Indications for Monitoring in Intensive Care Setting

- Patients with severe acute pancreatitis
- Patients with acute pancreatitis and one or more of the following:
  - Pulse <40 or >150 beats per minute
  - Systolic arterial pressure <80 or mean arterial pressure <60 mm Hg or diastolic arterial pressure >120 mm Hg
  - Respiratory rate >35 breaths per minute
  - Serum sodium <110 or >170 mg/dL
  - Serum Potassium <2 or >7 mg/dL
  - Pa_{O_2} <50 mm Hg
  - pH <7.1 or >7.7
  - Serum glucose >800 mg/dL
  - Serum calcium >15 mg/dL
  - Anuria
  - Coma

Prediction of Severity

Early prediction of severity in acute pancreatitis is important for identifying patients at increased risk of morbidity and mortality. This can be challenging, as there is no single, reliable way to predict severity. Current severity indices are based on clinical and radiographic parameters. An important clinical factor in determining severity is the persistence of organ failure for more than 48 hours. Various grading and scoring systems have been developed for risk-stratifying patients with acute pancreatitis. Historically, the Ranson criteria and Glasgow scoring systems were used, but these are cumbersome and can take up to 48 hours to complete. More recently, the APACHE II (Acute Physiology and Chronic Health Examination II) score has been used to predict severity in acute pancreatitis, although it is not pancreatitis-specific. Patients with an APACHE II score more than 8 usually have severe disease. A newer prognostic scoring system, the bedside index for severity in acute pancreatitis (BISAP), has been proposed as a simple method for early identification of patients at risk of in-hospital mortality and is as accurate as other scoring systems (Table 53.3). The BISAP assigns 1 point for each of the following signs within 24 hours of presentation: BUN level more than 25 mg/dL, impaired mental status, presence of SIRS, age more than 60 years, and pleural effusion on imaging studies. A BISAP score of 3 is associated with an increased risk of complications. Other single factors on admission associated with a severe course include hemoconcentration (hematocrit >44%), obesity, C-reactive protein (CRP) more than 150 mg/dL, albumin less than 2.5 mg/dL, calcium less than 8.5 mg/dL, BUN more than 20, and early hyperglycemia (Table 53.4). Markers of immune activation such as interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor (TNF) have also been associated with acute pancreatitis, although they are not routinely checked in clinical practice. Several studies have found BUN to be a good predictor of mortality in acute pancreatitis. A BUN more than 20 is associated with an increased risk of death, as is any increase in BUN at 24

hours postadmission. The computed tomography severity index (CTSI) is a scoring system based on contrast-enhanced CT grading system (A-E) and the percentage of pancreatic necrosis (Table 53.5). Pancreatic necrosis appears as a sharp demarcated region that does not enhance after intravenous contrast. A score more than 6 indicates severe disease and a poorer prognosis. There are a variety of local complications that can be diagnosed on cross-sectional imaging in severe acute pancreatitis. Early findings include pancreatic necrosis and acute fluid collections, which are almost always sterile. Other complications that can occur at various stages include peripancreatic artery pseudoaneurysm (eg, gastroduodenal, hepatic, and splenic arteries) and venous thrombosis (eg, portal, superior mesenteric, and splenic veins). Pancreatic necrosis can be sterile (Figure 53.1A) or infected (Figure 53.1B). Infected necrosis is a delayed complication, generally occurring more than 2 weeks after symptom onset; however, early cases of infected necrosis have been reported. Persistent fevers, leukocytosis, and hemodynamic instability associated with gas within the necrotic area are clinical indicators of infected necrosis. Patients with gas-containing pancreatic necrosis who are hemodynamically stable likely have developed a pancreatico-enteric fistula. The diagnosis can be confirmed with needle aspiration of the necrotic area, but the decision to proceed with invasive treatment is based on the patient's overall stability. Stable patients, even with infected necrosis, can be managed conservatively without drainage.

TABLE 53.3 BISAP Score for Predicting Severity and Complications in Acute Pancreatitis

- BUN >25
- Impaired mental status
- Systemic inflammatory response
- Age >60 years
- Pleural effusion

Calculate within 24 h; increased risk for complications in patients with score of 3 or more.
BISAP, bedside index for severity in acute pancreatitis; BUN, blood urea nitrogen.

TABLE 53.4 Other Single Factors on Admission Associated With Severe Acute Pancreatitis

- Hematocrit >44%
- Obesity
- C-reactive protein (CRP) >150 mg/dL
- Albumin <2.5 mg/dL
- Calcium <8.5 mg/dL
- Early hyperglycemia

TABLE 53.5 Computed Tomography (CT) Grading of Acute Pancreatitis: CT Severity Index

Grade[a]	Findings	Score
A	Normal pancreas: normal size, sharply defined, smooth contour, homogeneous enhancement, retroperitoneal peripancreatic fat without enhancement	0
B	Focal or diffuse enlargement of the pancreas; contour may show irregularity, enhancement may be inhomogeneous, but there is no peripancreatic inflammation	1
C	Peripancreatic inflammation with intrinsic pancreatic abnormalities	2
D	Intrapancreatic or extra-pancreatic fluid collections	3
E	Two or more large collections of gas in the pancreas or retroperitoneum	4
Necrosis Score Based on Contrast-Enhanced CT		

Grade[a]	Findings	Score
Necrosis (%)	Score	
0	0	
<33	2	
33-50	4	
>50	6	

CT severity index equals unenhanced CT score plus necrosis score: maximum = 0, ≥6 = severe disease.
[a]Grading based on findings on unenhanced CT.

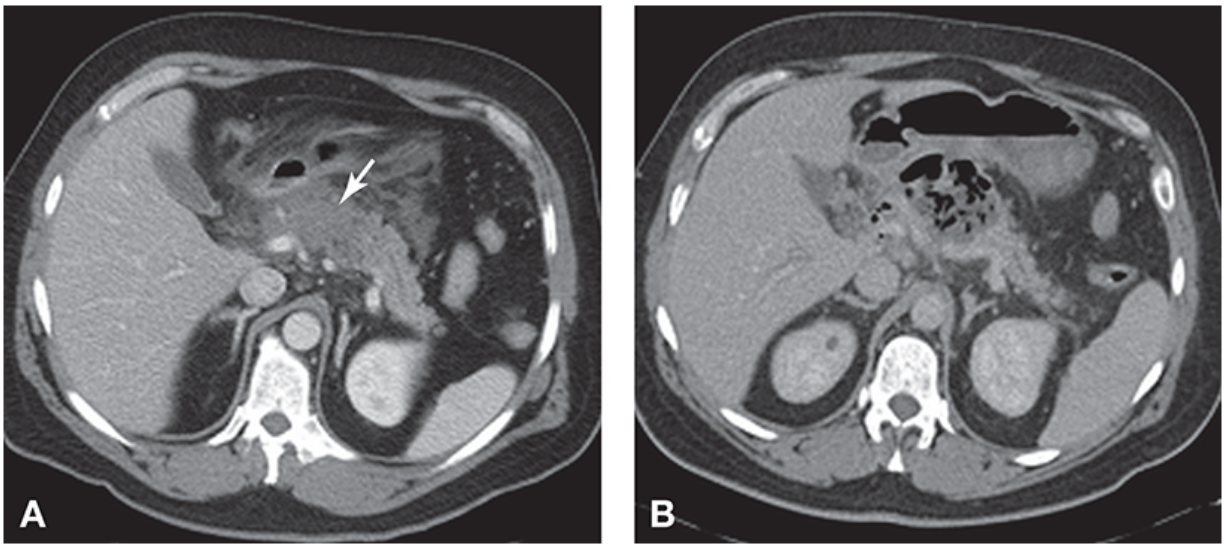

FIGURE 53.1 **A:** Necrotizing pancreatitis. Area of decreased attenuation in the pancreatic head and neck (*arrow*) represents necrosis in a patient with severe ethanol-induced pancreatitis. The body and tail are viable. **B:** Imaging in the same patient several weeks after presentation with gas within the fluid collection indicating infected necrosis.

The revised Atlanta Classification (2012) recognized three levels of severity of acute pancreatitis: mild, moderately severe, and severe (Table 53.6). In mild pancreatitis, there are no local or systemic

complications or organ failure. These patients typically recover with supportive care within a week without complications. Patients with moderately severe acute pancreatitis have transient organ failure that resolves within 48 hours or a local complication such as a pancreatic fluid collection without persistent organ failure. Severe acute pancreatitis is defined by more than 48 hours of persistent organ failure. Persistent organ failure has been found to be associated with a 33% risk of mortality.

TABLE 53.6 Revised Atlanta Classification of Acute Pancreatitis Definitions of Severity

Mild

- No organ failure
- No local or systemic complications

Moderately Severe

- Organ failure that resolves within 48 h (transient)
- Local or systemic complications without persistent organ failure

Severe

- Persistent organ failure (>48 h): single organ or multiple organ failure

Management

This section will address the treatment strategies in severe acute pancreatitis, including intravenous fluids (IVF), pain control, nutritional support, the role of ERCP, use of antibiotics, and management of peripancreatic fluid collections (Table 53.7). Hypovolemia is thought to be the principal etiology of pancreatic hypoperfusion and inflammation in acute pancreatitis. Thus, rapid restoration of intravascular volume is the first and most effective therapy. Fluid resuscitation helps maintain intravascular volume in the setting of massive capillary leak associated with the inflammatory response to acute pancreatitis. Fluid resuscitation prevents local ischemia and the development of pancreatic necrosis, SIRS, and

multiorgan failure. Recommendations regarding fluid rate, type, and duration may vary and should be individualized, although most studies have shown that early hydration within the first 24 hours decreases morbidity and mortality. In general, all patients suspected of having acute pancreatitis should be treated aggressively, as if they have severe disease, until proven otherwise. Previously, aggressive hydration was considered the cornerstone of management, but recent data suggest that moderate resuscitation may have the same benefits and prevent more volume overload. However, it still may not prevent progression to more severe forms of pancreatitis.

TABLE 53.7 Management of Severe Acute Pancreatitis in the Intensive Care Unit

- Supportive care: aggressive IVF, pain control
- Early ERCP (<48-72 h) in patients with suspected concurrent cholangitis or biliary obstruction
- Early enteral nutrition via nasojejunal tube
- No role for antibiotics in infection prophylaxis
- Reserve drainage[a] for:
  - Acute fluid collections with abdominal compartment syndrome
  - Suspected infected necrosis in an unstable patient (usually occurs 2-3 wk into illness)

[a]Current evidence supports “step-up” approach to peripancreatic fluid collections and infected necrosis (endoscopic or percutaneous drainage initially followed by surgery if necessary).
IVF, intravenous fluid; ERCP, endoscopic retrograde cholangiopancreatography.

At the very least, a patient presenting with acute pancreatitis should be started on IVF at a rate of 250 to 300 mL/h in order to maintain a urine output of at least 0.5 mL/kg/h. In patients with signs of severe volume depletion, maximal fluid resuscitation of 500 to 1,000 mL/h should be initiated and can be decreased once evidence of hypoperfusion subsides. The American College of Gastroenterology guidelines recommend goal-directed fluid

resuscitation with 250 to 500 mL/hr of isotonic crystalloid for the first 12 to 24 hours, with frequent reevaluation every 6 hours. The therapeutic goal is to decrease the BUN level from the admission value. In a randomized study, the use of lactated Ringers (LR) solution decreased the length of hospital stay, intensive care unit (ICU) admission, and pancreatic necrosis. However, the use of LR did not show a difference in SIRS score at 24 hours. Care should be taken to avoid using LR on patients with hypercalcemia, as this solution contains calcium. Although routine use of invasive intravascular monitoring is not routinely recommended, it may be useful in severe disease. With the cardinal symptom of acute pancreatitis being severe epigastric abdominal pain, intravenous opiate pain medication should be administered. It may be necessary to administer pain medications via a patient-controlled anesthesia (PCA) pump to ensure adequate pain control, as uncontrolled pain can contribute to hemodynamic instability. Nausea and vomiting associated with pancreatitis usually respond well to parenteral antiemetics. Patients with mild pancreatitis should begin eating as soon as they feel able. Multiple studies have demonstrated that early feeding is associated with decreased length of stay, progression of pancreatitis, and ICU admissions. In patients with severe pancreatitis, enteral nutrition is preferred over total parenteral nutrition. Enteral nutrition preserves the intestinal mucosa, potentially reducing the incidence of bacterial translocation from the gut and subsequent infectious complications. Enteral nutrition is associated with reduced central line infections, sepsis, need for surgical intervention, length of hospital stay, and mortality when compared to total parenteral nutrition. However, there is no consensus on the preferred route of enteral nutrition, for example, oral versus gastric versus postpyloric feeding. A randomized controlled trial demonstrated that early nasoenteric tube feeding was not different from an oral diet started at 72 hours in reducing rates of infection or death in patients with acute pancreatitis at high risk of complications. In clinical practice, nasogastric or nasoenteric feeding options should generally be initiated within 72 hours of admission in patients who are unable to advance their diets on their own.

In cases of gallstone pancreatitis, antibiotics should be initiated, and biliary decompression via ERCP should be performed early (within the first 72 hours) if ascending cholangitis is suspected. In situations where patients are too unstable for sedation or when ERCP is unavailable, a percutaneous transhepatic cholangiogram (PTC) with catheter placement can be performed. Early ERCP does little to affect the course of pancreatitis but reduces morbidity associated with concurrent cholangitis. If a patient with acute pancreatitis has abnormal liver enzymes and an intact gallbladder, cholecystectomy should be performed during the same hospital stay or within 30 days of discharge to decrease the risk of recurrent acute pancreatitis. An ERCP with biliary sphincterotomy should be performed in patients who are not surgical candidates. In general, routine use of prophylactic antibiotics is not recommended in severe pancreatitis. Antibiotics are recommended if there is a concern for concurrent cholangitis or for other documented infections. Early in the course of disease, patients with severe pancreatitis can be febrile and have leukocytosis due to inflammation associated with pancreatitis alone, and antibiotics are not warranted for these signs alone. Antibiotics should not be given routinely in necrotizing pancreatitis since infected necrosis is a late complication, generally occurring at least 2 weeks after symptom onset. Overall, antibiotics may decrease infectious complications but have not been shown to decrease mortality. Treatment with antibiotics is appropriate when documented positive blood cultures and/or fine needle aspiration of pancreatic necrosis reveal infection. The preferred antibiotics for pancreatic necrosis are carbapenems, quinolones, or metronidazole, because these antibiotics penetrate the necrotic pancreas. Probiotics have no role in the management of severe pancreatitis. Local complications of acute pancreatitis include peripancreatic fluid collection, pancreatic pseudocyst, necrotic fluid collections, and walled-off necrosis (Table 53.8). Acute fluid collections (enzyme-rich pancreatic fluid and tissue debris in and around the pancreas) occur in up to 40% of patients with severe pancreatitis. They represent a serous or exudative reaction to pancreatic injury and inflammation. There is little role for draining acute fluid collections unless

abdominal compartment syndrome, severe gastric outlet obstruction, or early infection is suspected. The majority of acute fluid collections resolve spontaneously.

TABLE 53.8 Pancreatic Fluid Collections

Acute Peripancreatic Fluid Collection
- Associated with interstitial, edematous pancreatitis and no necrosis
- Occur within first 4 wk
- No wall or encapsulation

Pancreatic Pseudocyst
- Well circumscribed with well-defined wall
- No nonliquid component
- Maturation requires >4 wk after onset of acute pancreatitis

Acute Necrotic Collection
- Occurs in setting of acute necrotizing pancreatitis
- Heterogeneous and nonliquid components
- No definable wall

Walled-Off Necrosis
- Heterogeneous with nonliquid components
- Encapsulated
- Maturation requires 4 wk after onset of acute necrotizing pancreatitis

There is consensus agreement that drainage of pancreatic necrosis is indicated when the necrosis becomes infected or in patients with sterile necrosis who remain clinically unwell. Infected necrosis is suspected when there is gas within the collection on cross-sectional imaging as well clinical signs of fever, bacteremia, or clinical deterioration. These signs/symptoms may be difficult to differentiate from worsening sequelae of pancreatitis; however, they should prompt consideration of antibiotic treatment. It must be noted that multiple trials have not demonstrated any clinical benefit of prophylactic antibiotic administration in terms of preventing the development of infected necrosis, systemic complications, or mortality. Delayed drainage of peripancreatic fluid collections is preferred and has been associated with a reduced length of hospital stay, pancreatic fistula, and need for future interventions Previously,

surgical intervention and debridement or a percutaneous approach were the mainstays of therapy, but an endoscopic approach is now favored. Percutaneous drainage should be considered when endoscopic drainage is unavailable or not technically feasible. Patients in the early stage of acute necrotizing pancreatitis with infected necrosis, whose collections are ill-defined, may benefit from percutaneous drainage. Numerous studies have also shown that percutaneous drainage is indicated when the fluid collection or necrosis extends into the paracolic gutters, as drainage through trans-enteric stents is not as effective in these nondependent areas. Typically, lumen-apposing metal stents have been the most commonly used stents for the drainage of peripancreatic fluid collections. They provide a wide diameter, allowing for increased drainage and easier direct endoscopic necrosectomy. They have been shown to have a higher technical and clinical success for the management of walled-off necrosis than either fully covered metal stents or plastic double-pigtail stents. However, lumen-apposing metal stents are expensive, associated with an increased risk of bleeding, and the optimal indwell time is still unknown. Unstable patients with infected necrosis or abdominal compartment syndrome usually require drainage. Traditionally, this has been accomplished with exploratory laparotomy, debridement, and drain placement, but is associated with high morbidity and mortality. There is now compelling evidence that endoscopic or percutaneous drainage results in lower morbidity and mortality than open surgery; therefore, there has been a move toward delayed intervention and minimally invasive approaches, including direct endoscopic pancreatic necrosectomy and percutaneous drainage.

Summary

Acute pancreatitis is a frequently encountered medical condition requiring hospital admission and is associated with high rates or morbidity and mortality. Numerous scoring systems have been used to predict disease severity and direct medical treatments.

Early diagnosis and aggressive medical management with IVF, pain control, and early feeding are paramount to improving patient outcomes.

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SECTION XIV NEUROLOGIC DISORDERS

54 Status Epilepticus

Casey Dunn

Definition of Status Epilepticus

Status epilepticus (SE) was redefined by the International League Against Epilepsy (ILAE) in 2015 based upon two important time points (t1 and t2). Time point t1 indicates when treatment should be initiated for abnormally long seizures. Time point t2 indicates the duration of seizure that can lead to long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks. SE has two primary clinical phenotypes: convulsive and nonconvulsive. Convulsive SE is defined by prominent motor phenomenon classified as tonic-clonic, myoclonic, focal motor, tonic, or hyperkinetic. Nonconvulsive SE is defined by not having any prominent motor phenomenon. Electrographically, both clinical phenotypes may have either focal or generalized seizures. In convulsive SE, time point t1 is around 5 minutes as most convulsive seizures will stop without treatment within 2 to 3 minutes. Time point t1 for nonconvulsive SE is not well defined. The ILAE currently suggests initiating treatment after 10 minutes for these patients. When considering time point t2, patients with convulsive SE reach the point of having long-term consequences after 30 minutes of seizing. The point of suffering permanent neuronal injury is not well defined in nonconvulsive patients. Aggressive prompt intervention (especially for convulsive seizures) is paramount. SE occurs in over 100,000 persons each year in the United States. Causes of SE can be divided into acute processes, either in the central nervous system or systemically, or chronic disorders such as preexisting epilepsy or an old stroke or brain tumor (Table 54.1). It is imperative to evaluate and manage the underlying etiology in parallel with attempts to control seizures.

TABLE 54.1 Causes of Status Epilepticus

Causes	Evaluation

Causes	Evaluation
Acute symptomatic CNS lesion Encephalitis/meningitis Cerebrovascular (ischemic stroke, ICH, SAH, CVST) Traumatic brain injury Global hypoxic-ischemic brain injury (post–cardiac arrest) Hypertensive encephalopathy/PRES	Brain imaging (head CT, MRI) Lumbar puncture
Chronic CNS lesion Existing stroke Brain tumor (primary or metastatic) Vascular malformation	Brain imaging (head CT, MRI)
Toxic/metabolic derangement: Drug intoxication or overdose (TCA, amphetamine) Drug withdrawal (alcohol, benzodiazepines) Iatrogenic: medications (beta-lactams, theophylline, others) Hypoglycemia with or without hyperglycemia Electrolytes (hyponatremia, hypocalcemia) Febrile seizures (in young children)	Drug screen and drug history, EKG Glucose level Electrolytes
Epilepsy Noncompliance with AEDs Recent change in dose or AED Psychogenic seizures	Medication history Serum AED levels
Rare Autoimmune or paraneoplastic encephalitis Mitochondrial diseases Genetic disorders	Lumbar puncture Serum and CSF AIE panels Muscle biopsy

AEDs, antiepileptic drugs; AIE, autoimmune encephalitis; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CVST, cerebral venous sinus thrombosis; EKG, electrocardiogram; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage; TCA, tricyclic antidepressant.

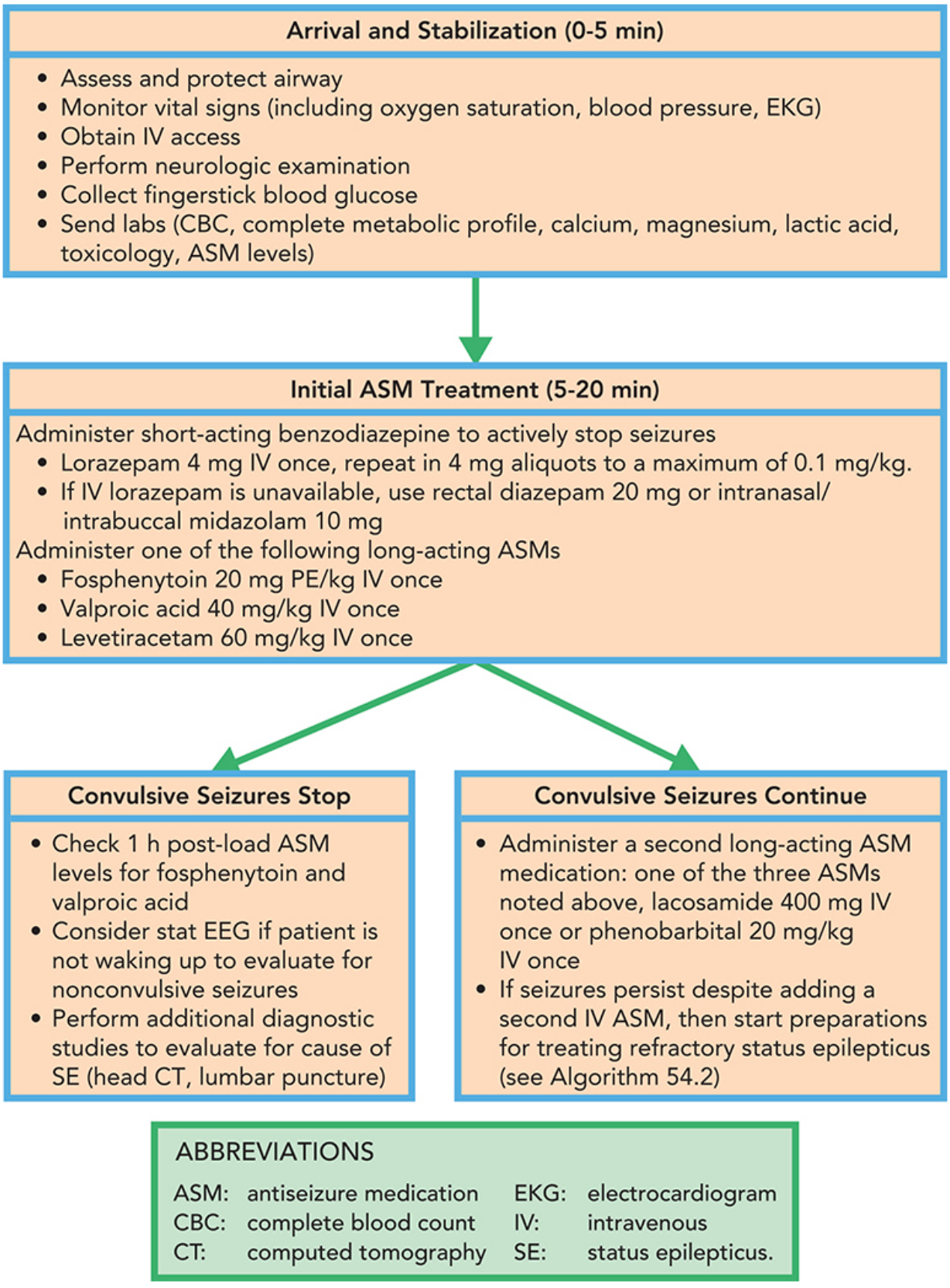
Initial Management of Status Epilepticus

The first priorities are stabilization of the airway, breathing, and circulation. Not all patients with incipient SE require intubation, but all require close attention to patency of the airway. The head should be positioned to avoid obstruction, and an artificial airway may be placed. Placing an oral airway may be

challenging in a patient with teeth clenched, but a nasal airway can usually be inserted. Oxygen can be applied via nasal cannula or face mask. Many patients with SE will maintain oxygen saturation with these basic measures and continue to ventilate. It is common for patients with seizures to develop an acute lactic acidosis that resolves as SE is controlled. Hypertension is more common than hypotension in the early stages of SE, while hemodynamic support and invasive monitoring are often required later as treatment intensifies.

Benzodiazepines are the recommended first-line agents to stop abnormally long seizures (Algorithm 54.1). Lorazepam should be given in 4 mg aliquots and repeated every 3 minutes to a maximum of 0.1 mg/kg intravenously (IV). If IV access is not immediately available, then rectal diazepam gel (Diastat: 0.2 mg/kg in adults, usually 10-20 mg) can be used. Midazolam can also be squirted into the mouth or delivered intranasally (10 mg, with rapid absorption by both routes). Such rapidly acting agents will be effective in 50% or more of SE cases treated early. However, the duration of anticonvulsant action of these agents is relatively short (longest for lorazepam).

ALGORITHM 54.1 **Initial Treatment of Status Epilepticus**


Arrival and Stabilization (0-5 min)
• Assess and protect airway
• Monitor vital signs (including oxygen saturation, blood pressure, EKG)
• Obtain IV access
• Perform neurologic examination
• Collect fingerstick blood glucose
• Send labs (CBC, complete metabolic profile, calcium, magnesium, lactic acid, toxicology, ASM levels)
Initial ASM Treatment (5-20 min)
Administer short-acting benzodiazepine to actively stop seizures
• Lorazepam 4 mg IV once, repeat in 4 mg aliquots to a maximum of 0.1 mg/kg.
• If IV lorazepam is unavailable, use rectal diazepam 20 mg or intranasal/ intrabuccal midazolam 10 mg
Administer one of the following long-acting ASMs
• Fosphenytoin 20 mg PE/kg IV once
• Valproic acid 40 mg/kg IV once
• Levetiracetam 60 mg/kg IV once
Convulsive Seizures Stop
• Check 1 h post-load ASM levels for fosphenytoin and valproic acid
• Consider stat EEG if patient is not waking up to evaluate for nonconvulsive seizures
• Perform additional diagnostic studies to evaluate for cause of SE (head CT, lumbar puncture)
Convulsive Seizures Continue
• Administer a second long-acting ASM medication: one of the three ASMs noted above, lacosamide 400 mg IV once or phenobarbital 20 mg/kg IV once
• If seizures persist despite adding a second IV ASM, then start preparations for treating refractory status epilepticus (see Algorithm 54.2)
ABBREVIATIONS
ASM: antiseizure medication
CBC: complete blood count
CT: computed tomography
EKG: electrocardiogram
IV: intravenous
SE: status epilepticus.

A longer acting antiseizure medication (ASM) should be given concurrently or immediately after benzodiazepines in cases of SE. IV fosphenytoin, levetiracetam, and valproic acid were shown in a randomized controlled trial to stop seizures and improve mental status at similar rates in nearly 50% of patients. **Fosphenytoin** is a prodrug that is converted to phenytoin and is dosed in "phenytoin equivalents" or PE. It can be given at a rate of 150 mg PE per minute through a peripheral IV with less potential for arrhythmias or hypotension than IV phenytoin. Initial IV fosphenytoin load should be 20 mg PE/kg with a maximum of 1,500 mg PE. **Valproic acid** is dosed at 40 mg/kg with a maximum dose of 3,000 mg. It should be infused at a maximum rate of 10 mg/kg/min. **Levetiracetam** is dosed at 60 mg/kg with a maximum of 4,500 mg. It is infused at a maximum rate of 100 mg/min. Other IV ASMs such as phenobarbital or lacosamide are also considered reasonable alternatives for initial long-term seizure control. **Phenobarbital** is dosed at 20 mg/kg with a maximum infusion rate of 50 to 70 mg/min. **Lacosamide** is dosed with a single 400 mg IV dose over 5 minutes when used in SE. Cardiac arrhythmia is a possibility with lacosamide, so be certain to review an EKG for evidence of PR prolongation if considering treatment (see Algorithm 54.1).

After loading with IV fosphenytoin, valproic acid, or phenobarbital, it is important to check therapeutic levels for these medications 1 hour post IV load to ensure that adequate therapeutic levels are achieved. A phenytoin level should be sent after loading with fosphenytoin with goal total blood levels of 15 to 25 mcg/mL. The valproate level goal is a total blood level of 70 to 100 mcg/mL. The phenobarbital level goal is a total blood level of 20 to 40 mcg/mL. There is no need to check a post-load level for levetiracetam or lacosamide. Be certain to use appropriate loading doses as underdosing increases the likelihood that seizures will persist.

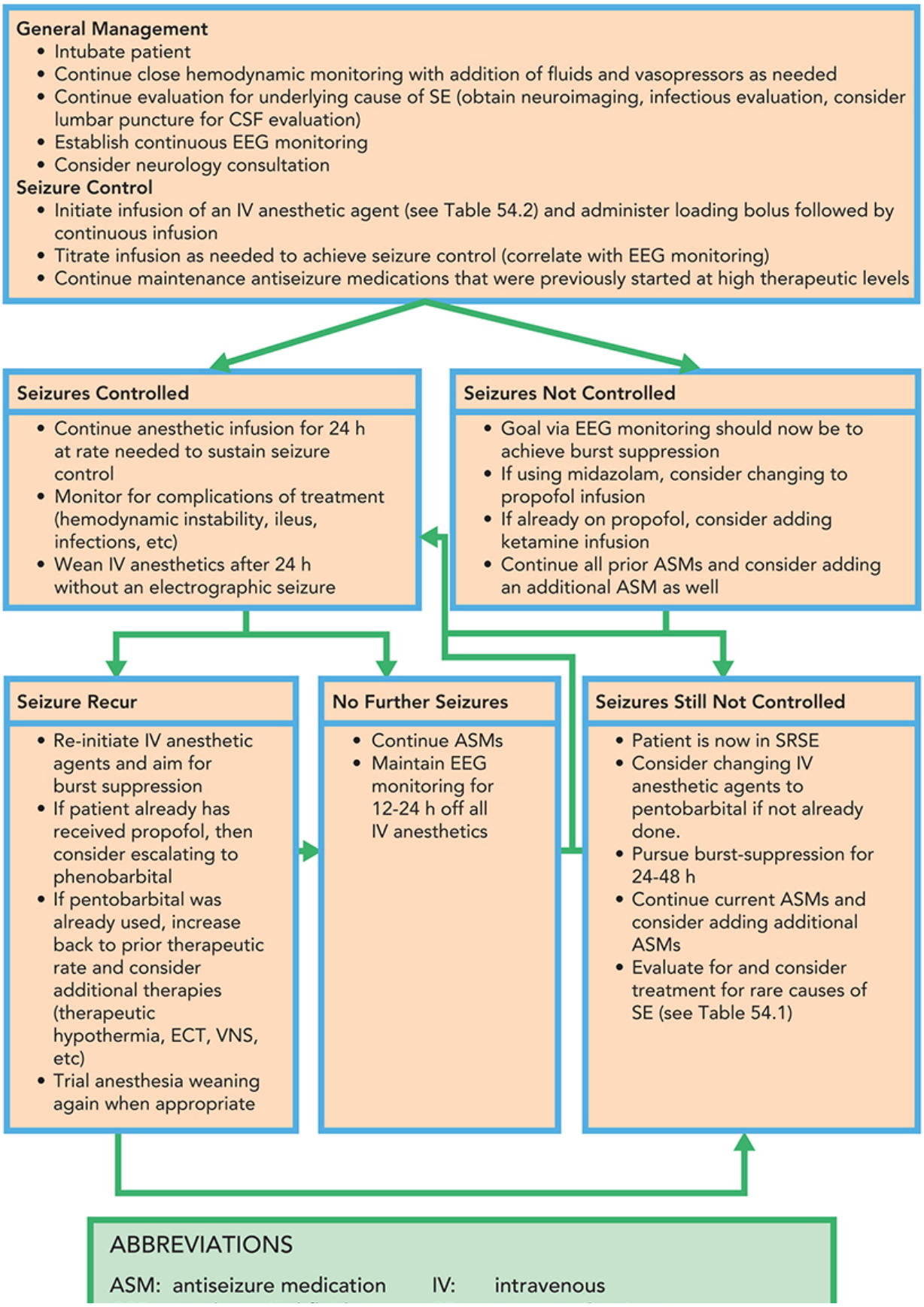
Once the initial IV dose is given, the ASM should be continued in order to prevent seizure recurrence. When using fosphenytoin, valproic acid, or phenobarbital, the maintenance dose should be tailored to maintain the therapeutic levels discussed earlier. When using levetiracetam, the total maintenance dose ranged from 2 to 4 g daily split between two doses. The dose should be tailored to the patient's renal function. For lacosamide, the total maintenance dose is 200 to 400 mg daily split between two doses.

Refractory Status Epilepticus

A subset of patients presenting with SE (20%-40%) will fail to respond to initial adequate dosing of IV benzodiazepines and IV ASM load. By this time,

seizures will have usually persisted for 30 to 60 minutes, if not longer. This subgroup is designated to have *refractory status epilepticus* (RSE). This carries a significantly higher mortality and worse functional outcome. Most will require continuous infusions of anesthetic anticonvulsants to control RSE (although an additional nonanesthetic agent can be given for focal RSE without significantly impaired level of consciousness before initiating aggressive anesthetic agents). Patients receiving deep sedation to control RSE need to be admitted to the intensive care unit and usually require both ventilatory support and electroencephalogram (EEG) monitoring (Algorithm 54.2). If intubation is required, the use of paralytics should ideally be avoided or restricted to short-acting agents so as not to mask ongoing convulsive movements. SE that begins with convulsions (eg, generalized tonic-clonic seizures) often evolves into a state of dissociation between ongoing electrical seizure activity and lack of obvious motor expression; such nonconvulsive RSE requires EEG to diagnose and monitor its treatment. Subtle motor manifestations may be observed, including facial myoclonus, tonic eye deviation, or nystagmus. Continuous EEG with video monitoring is preferable to correlate electrographic changes with states of arousal, clinical manifestations, and stimulation.

ALGORITHM 54.2 **Treatment of Refractory and Super-Refractory Status Epilepticus**


General Management
• Intubate patient
• Continue close hemodynamic monitoring with addition of fluids and vasopressors as needed
• Continue evaluation for underlying cause of SE (obtain neuroimaging, infectious evaluation, consider lumbar puncture for CSF evaluation)
• Establish continuous EEG monitoring
• Consider neurology consultation
Seizure Control
• Initiate infusion of an IV anesthetic agent (see Table 54.2) and administer loading bolus followed by continuous infusion
• Titrate infusion as needed to achieve seizure control (correlate with EEG monitoring)
• Continue maintenance antiseizure medications that were previously started at high therapeutic levels
Seizures Controlled
• Continue anesthetic infusion for 24 h at rate needed to sustain seizure control
• Monitor for complications of treatment (hemodynamic instability, ileus, infections, etc)
• Wean IV anesthetics after 24 h without an electrographic seizure
Seizures Not Controlled
• Goal via EEG monitoring should now be to achieve burst suppression
• If using midazolam, consider changing to propofol infusion
• If already on propofol, consider adding ketamine infusion
• Continue all prior ASMs and consider adding an additional ASM as well
Seizure Recur
• Re-initiate IV anesthetic agents and aim for burst suppression
• If patient already has received propofol, then consider escalating to phenobarbital
• If pentobarbital was already used, increase back to prior therapeutic rate and consider additional therapies (therapeutic hypothermia, ECT, VNS, etc)
• Trial anesthesia weaning again when appropriate
No Further Seizures
• Continue ASMs
• Maintain EEG monitoring for 12-24 h off all IV anesthetics
Seizures Still Not Controlled
• Patient is now in SRSE
• Consider changing IV anesthetic agents to pentobarbital if not already done.
• Pursue burst-suppression for 24-48 h
• Continue current ASMs and consider adding additional ASMs
• Evaluate for and consider treatment for rare causes of SE (see Table 54.1)
ABBREVIATIONS
ASM: antiseizure medication
IV: intravenous

CSF:	cerebrospinal fluid	SE:	status epilepticus
ECT:	electroconvulsive therapy	SRSE:	super-refractory status epilepticus
EEG:	electroencephalogram	VNS:	vagus nerve stimulator.

Choice of anesthetic agent to control RSE is not guided by rigorous comparative evidence. It should be based on a consideration of patient factors, including hemodynamic stability, seizure severity and duration, and goal of treatment, as well as local (physician and institutional) experience. The major choices are compared in Table 54.2. The majority of these medications target GABA receptors that are the major inhibitory receptors in brain cells. These medications can be titrated to achieve either seizure cessation (lack of any electrographic seizures) or burst suppression (periods of electrographic silence interspersed with brief "bursts" of electrical activity). Various retrospective studies have not identified any difference in mortality between the two strategies. **Midazolam** is a reasonable first-line option for RSE if EEG seizure cessation is the target. **Propofol** is most often used when midazolam is unable to achieve seizure suppression or if burst suppression is the target of therapy. **Pentobarbital** is most often reserved for cases of super-refractory status epilepticus (SRSE) rather than as a first-line anesthetic for RSE.

TABLE 54.2 Anesthetic Infusions for Refractory Status Epilepticus

	Midazolam	Propofol	Pentobarbital	Ketamine	Volatile Anesthetics
Mechanism	Benzodiazepine (GABA)	Unclear (GABA modulation)	Barbiturate (GABA)	NMDA antagonist	Polysynaptic GABA
Loading dose[a]	0.2 mg/kg	1-2 mg/kg	5 mg/kg	1-2 mg/kg	NA
Starting infusion	0.05 mg/kg/h	1-2 mg/kg/h (15-30 mcg/kg/min)	1 mg/kg/h	0.5 mg/kg/h	NA
Infusion range	0.05-0.8 mg/kg/h	1-15 mg/kg/h (15-250 mcg/kg/min)	0.5-10 mg/kg/h	0.5-10 mg/kg/h	0.8%-2.0%
Half-life	1-2 h[b]	<1 h[b]	15-40 h	2.5 h	<1 h

	Midazolam	Propofol	Pentobarbital	Ketamine	Volatile Anesthetics
Adverse effects	Hypotension Tachyphylaxis	Hypotension "Infusion syndrome" Lipemia	Hypotension Bradycardia Poikilothermia Pulmonary infections		Hypotension Ileus

[a]May repeat loading dose boluses until seizures controlled.
[b]May accumulate with prolonged infusions.

As SE progresses over the first few hours, brain cells start to internalize inhibitor GABA receptors while externalizing excitatory AMPA and NMDA receptors. **Ketamine** is an NMDA antagonist that may, therefore, provide benefit for patients who have not achieved seizure suppression with GABA agonist alone. Some patient series have found improved seizure control with the addition of ketamine for at least 24 hours. Most importantly, patients in these series were also found to have no significant changes in intracranial pressure, cerebral perfusion pressure, or cerebral blood flow while being treated with ketamine. Volatile anesthetics have been used in limited series and require specialized equipment and monitoring. Their major advantages are short half-life and ability to rapidly induce burst suppression.

Many patients requiring deep sedation will develop hypotension requiring fluid resuscitation and vasopressor support. There is a definite risk of "propofol-related infusion syndrome (PRIS)" with the high cumulative doses of propofol often required to control RSE. PRIS manifests as a variable combination of metabolic acidosis, hyperkalemia, rhabdomyolysis, renal failure, bradycardia, and arrhythmias (including cardiac arrest). Respiratory drive will be severely inhibited or abolished, and all patients require mechanical ventilation with meticulous attention paid to prevention of ventilator-associated pneumonia and other nosocomial infections. If background levels of antiepileptic drugs (AEDs) are not maintained, then seizures will recur when anesthetic agents are weaned off. Phenytoin, fosphenytoin, levetiracetam, lacosamide, valproate, topiramate, and/or other agents should be continued and titrated in patients with RSE during and after the use of anesthetic infusions. Patients treated with phenytoin, valproate, phenobarbital, and carbamazepine should have levels monitored frequently, if possible, with a therapeutic target in the high therapeutic range.

Super-Refractory Status Epilepticus

SRSE occurs in 9% of patients with SE. It is defined as SE that either persists at least 24 hours after the onset of IV anesthetic treatment or recurs while IV anesthetic agents are being weaned. Treatment initially consists of pursuing deeper and longer sedation with the goal of achieving burst suppression. Primary options for treatment include utilizing propofol and ketamine infusions in concert or changing to a pentobarbital infusion to achieve treatment goals. If these interventions fail, then hypothermia offers another treatment option in resistant cases where first-line anesthetic agents have failed or situations where the use of propofol or high-dose barbiturates is contraindicated. This has only been shown to be effective in a small series where temperature was lowered to between 31 and 35 °C and titrated to EEG response. The major advantage is rapid offset of metabolic suppression once temperature is normalized (in comparison to pentobarbital that persists for days after infusion is stopped). Other options for SRSE include induction of a ketogenic state with specialized feeding, the application of electroconvulsive therapy (ECT), vagus nerve stimulation (VNS) therapy, or neurosurgical resection of an epileptic lesion for patients with focal seizures. Evaluation for rare causes of SE (see Table 54.1) should take place for patients who develop SRSE with no prior history of seizures. Patients with SRSE due to autoimmune and paraneoplastic encephalitis can experience significant benefit from immunotherapies, such as steroids, intravenous immunoglobulin (IVIG), or plasmapheresis.

Therapy De-Escalation

Once the EEG treatment goal has been achieved (ie, seizure cessation and/or burst suppression), it may be advisable to maintain infusion rates and EEG targets for 24 hours before gradually weaning. Avoidance of all epileptic activity on EEG (eg, periodic discharges) may not be necessary unless these are clearly associated with persistent alterations in mental status or build/evolve enough to resemble incipient seizures.

Prognosis

Nearly 50% of intensive care unit (ICU)-treated patients with RSE can recover to baseline function, while around 30% of patients will have new functional neurologic deficits. Mortality rates correlate with SE etiology and vary from 10% to 20% in convulsive RSE. Importantly, SRSE does not have a

necessarily poorer outcome. Factors associated with increased morbidity and refractoriness include older age, severely impaired consciousness, and cryptogenic causes of SRSE. Young patients with RSE/SRSE (even those requiring a month or more of sedative therapies) may still make gratifying recoveries if ICU complications are avoided and the underlying source of seizures is reversible (eg, encephalitis) and treated successfully. SE in comatose survivors of cardiac arrest (ie, *postanoxic* SE) is usually an ominous sign of diffuse cerebral damage. Especially when accompanied by myoclonic jerking, the presence of SE is one of the most consistent predictors of death/nonrecovery after cardiac arrest. The one exception is when SE occurs in conjunction with a preserved brainstem examination and EEG shows evidence of reactivity. Postanoxic myoclonus and SE may be transiently controlled by agents, such as valproate, clonazepam, or levetiracetam, but SE is usually refractory, and aggressive measures should be withheld pending discussion of prognosis with the family.

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55 Acute Ischemic Stroke

Leeda Bashardost and Salah G. Keyrouz

Ischemic strokes represent about 87% of all strokes. It is the leading cause of serious long-term disability and is a major cause of death worldwide. Although most ischemic strokes can be managed on a regular hospital floor, some warrant admission to the intensive care unit (ICU). Patients who are treated with thrombolytics and/or mechanical thrombectomy are admitted to a specialized stroke or ICU for tight blood pressure control and monitoring for hemorrhagic and other complications. Large hemispheric, cerebellar, or brainstem strokes require frequent neurologic monitoring in a critical care setting given the potential need for osmotic therapy, cerebrospinal fluid (CSF) diversion, or surgical decompression to treat cerebral edema. In addition, decreased alertness and weak bulbar muscle tone may lead to respiratory compromise necessitating airway management and mechanical ventilation. Lastly, the underlying stroke etiology could pose management challenges that need to be dealt with in an ICU, like arrhythmias, myocardial infarction, endocarditis with valvular dysfunction, and hypertensive emergencies to name a few.

Presentation

Ischemic strokes occur when there is sudden inadequate perfusion to a brain region causing neuronal death and irreversible damage. Clinical presentation varies and depends on the affected brain region. Symptoms may be as subtle as minor sensory loss or major motor and/or speech impairment. Thalamic and brainstem infarctions may cause alteration of mental status that may be difficult to distinguish from metabolic or infectious encephalopathy. Clinical

diagnosis is usually possible when acute deficits match the pattern of a typical stroke syndrome. A suspicion of stroke should always prompt the clinician to perform head computed tomography (CT) or magnetic resonance imaging (MRI) to exclude intracranial hemorrhage and evaluate the presence of other structural lesions, such as neoplasia or abscess ("stroke mimics"). Other pathologies that may mimic stroke include postictal neurologic deficits (typically paralysis), complicated migraine, metabolic derangements (eg, hypo or hyperglycemia), and psychosomatic disorders.

Management

INTRAVENOUS THROMBOLYSIS AND MECHANICAL THROMBECTOMY

For ischemic strokes within 4.5 hours from onset, intravenous (IV) thrombolysis with alteplase or tenecteplase is the intervention of choice in select patients (Table 55.1). However, critically ill patients with multiple failing organs are seldom candidates for IV thrombolysis. This is often due to thrombocytopenia, coagulopathy, active bleeding, or failure to establish the time of last known normal, among other reasons. When eligibility criteria are met, IV thrombolytics should be administered as quickly as possible within the defined time frame for maximal benefit. Before administration, blood pressure should be lowered to less than 185/110 mm Hg. Prior aspirin or dual antiplatelet therapy is not a contraindication for IV thrombolysis. Patients receiving IV thrombolytics require 24 hours of monitoring for complications particularly intracranial hemorrhage (Table 55.2) and orolingual angioedema (Table 55.3). New neurologic changes should prompt brain imaging for assessment of hemorrhagic complications.

TABLE 55.1 Indications and Contraindications for Thrombolysis

Indications

1. Acute onset of focal neurologic symptoms in a defined vascular territory, consistent with ischemic stroke
2. Clearly defined onset of stroke <3 or 4.5 h prior to planned start of treatment (if patient awakens with symptoms, onset is defined as “last seen normal”)
3. Age 18 or older
4. No evidence of intracranial hemorrhage, nonvascular lesions (eg, brain tumor, abscess), or signs of advanced cerebral infarction such as sulcal edema, hemispheric swelling, or large areas of low attenuation consistent with acute stroke on CT

Contraindications

1. Onset of stroke >3 or 4.5 h (extended window) prior to planned start of treatment
2. Rapidly improving symptoms or mild, nondisabling symptoms (relative)
3. Seizure at onset of stroke symptoms (relative)
4. Clinical presentation suggestive of subarachnoid hemorrhage regardless of CT findings
5. Hypertension, SBP >185 mm Hg or DBP >110 mm Hg, resistant to antihypertensive therapy
6. Ischemic stroke within 3 mo
7. History of intracerebral or subarachnoid hemorrhage if recurrence risk is substantial
8. Known history of cerebral microbleeds (>10) demonstrated on MRI
9. Untreated cerebral aneurysm ≥10 mm or arteriovenous malformation
10. Gastrointestinal or genitourinary hemorrhage within the last 21 d
11. Gastrointestinal malignancy
12. Arterial puncture at a noncompressible site within 7 d
13. Lumbar puncture within 7 d (relative)
14. Aortic arch dissection
15. Major surgery or major trauma within the last 14 d (relative)
16. Intracranial or intraspinal surgery within 3 mo
17. Intra-axial intracranial neoplasm
18. Acute head injury
19. Severe head injury within 3 mo
20. Recent myocardial infarction in the past 3 mo (relative)
21. Acute pericarditis (relative)
22. Infective endocarditis

23. Patient taking oral anticoagulants (eg, warfarin, dabigatran [Pradaxa], rivaroxaban [Xarelto], apixaban [Eliquis])
24. Patient receiving heparin within 48 h or LMWH within 24 h
25. Received tPA <7 d previously
26. Known hemorrhagic diathesis or unsupported coagulation factor deficiency
27. Glucose <50 or >400 mg/dL
28. Platelet count <100,000/mm^3
29. INR >1.7 or elevated aPTT
30. Pregnancy (relative)

Additional contraindications for 3- to -4.5-h window

1. Severe stroke symptoms (NIHSS score >25)

[a]PTT, activated partial thromboplastin time; CT, computed tomography; DBP, diastolic blood pressure; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale/Score; SBP, systolic blood pressure; tPA, tissue plasminogen activator.

TABLE 55.2 Post-Thrombolysis Intracranial Hemorrhage Management

- Stop IV tPA infusion.
- Obtain an emergent CT Head.
- CBC, PT (INR), aPTT, fibrinogen level, type, and crossmatch
- Manage and treat elevated BP, monitor and treat hyperglycemia.
- Consider reversal of tPA:
  - Cryoprecipitate 10 U over 1 h, repeat dose if fibrinogen <150 mg/dL

    or
  - Tranexamic acid 1,000 mg IV over 1 h or epsilon-aminocaproic acid 4-5 g over 20 min
- Consider neurosurgical consultation.

aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; CT, computed tomography; INR, international normalized ratio; IV, intravenous; PT, prothrombin time; tPA, tissue plasminogen activator.

TABLE 55.3 Management of Adverse Reaction to IV Alteplase: Angioedema

- Stop IV tPA infusion.
- Monitor airway for intubation.
- Administer IV diphenhydramine 50 mg, IV ranitidine 50 mg, and IV methylprednisolone 125 mg.
- If worsening, consider epinephrine 0.3 mL subcutaneously or 0.5 mL nebulizer.
- Avoid ACE inhibitors.

ACE, angiotensin-converting enzyme; IV, intravenous; tPA, tissue plasminogen activator.

Mechanical thrombectomy should be offered to select patients with acute ischemic stroke, up to 24 hours from symptom onset, who have radiographic evidence of large vessel occlusion. CT perfusion or MRI with perfusion and diffusion-weighted images can be used to determine candidacy for extended window mechanical thrombectomy (6-24 hours from symptom onset).

POSTSTROKE MANAGEMENT

General critical care management is similar to that of other ICU patients: maintenance and restoration of normal acid-base physiology, oxygenation, euvolemia, and glycemic control. However, there are other considerations that are inherent to ischemic stroke victims. Fever has been shown to worsen outcomes in stroke, and effective temperature control likely mitigates this effect. The practice of permissive hypercapnia should be minimized if at all possible; the rise in CO_2 dilates intracranial vessels, especially arterioles, and leads to a rise in intracranial pressure, which could be detrimental in those with cerebral edema complicating large strokes. Aspirin (or another antiplatelet agent) should be given to patients with ischemic stroke within 24 to 48 hours after receiving thrombolytics. Combining clopidogrel and aspirin increases the odds of intra- and extracranial

hemorrhagic complications. Therefore, dual antiplatelet therapy in the immediate poststroke period should be avoided in the absence of a strong cardiac or cerebrovascular indication.

Heparin is no longer recommended for the treatment of acute ischemic stroke. There are rare occasions where it might be considered, for example, a cardiac or a carotid artery thrombus. Anticoagulation for atrial fibrillation reduces the chance of future stroke and is therefore indicated in instances of stroke or transient ischemic attacks. Generally, therapeutic anticoagulation is not started in the acute stroke period given the concern for hemorrhagic conversion. Depending on the size of the infarcted brain tissue, starting anticoagulation is recommended between 3 and 14 days poststroke. Mechanical and pharmacologic prophylaxis of venous thromboembolism should be initiated as soon as feasible. Enoxaparin is superior to unfractionated heparin in preventing deep venous thrombosis but not pulmonary embolism.

Stroke often causes reactive hypertension which helps to perfuse the ischemic penumbra. High blood pressure should be tolerated up to 220/120 mm Hg for the first 24 to 48 hours unless there is evidence of ongoing end-organ damage (eg, acute myocardial infarction, aortic dissection, heart failure, renal failure). If tissue plasminogen activator (tPA) was administered or mechanical thrombectomy resulted in recanalization, systolic and diastolic blood pressure are kept under 180 and 105 mm Hg, respectively, for the first 24 hours to avoid hemorrhagic complications. Commonly used antihypertensive drugs, such as IV beta-blockers or calcium channel blockers, are preferable because they are short-acting and rapidly titratable. Nitrates are avoided because of the risk of cerebral vasodilatation causing worsening edema. Inducing hypertension to salvage ischemic penumbra is a debated therapeutic approach and should only be utilized when a clear relationship between clinical deterioration and relatively low blood pressure is observed.

Determining the cause of stroke is necessary to guide therapy for secondary prevention. Telemetry, echocardiography, brain MRI, carotid Doppler study, and intracranial vascular imaging may be used. Given the increasing complexity of stroke management, proper

use and interpretation of these diagnostic tests should be done by or with the consultation of a stroke specialist. General methods of the past, such as universal anticoagulation and carotid endarterectomy, have changed to more complex algorithms and will likely evolve even further.

Cerebral Edema

The risk of cytotoxic cerebral edema and brain herniation is highest for patients with large cerebral and cerebellar infarctions. Young patients without age-related cerebral atrophy are at a particularly higher risk, necessitating close monitoring and aggressive interventions. Some infarctions may cause compression of the cerebral ventricular system and lead to obstructive hydrocephalus requiring a ventriculostomy. Edema will create pressure differentials between cerebral compartments created by dural folds leading to herniation syndromes. Cerebellar infarction is notorious for compressing the brainstem and fourth ventricle, thus causing hydrocephalus and catastrophic herniation. Edema typically peaks within 3 to 5 days, but in severe cases, rapid deterioration can occur within the first 48 hours with a mortality rate that approaches 80% to 90%. Risk factors for early deterioration include young age, large infarcts, and the use of thrombolytics. Simple measures such as keeping the head elevated at over 30°, avoiding hypotonic solutions which lead to hyponatremia and worsening cerebral edema, and careful monitoring may be sufficient. In cases with more severe edema, osmotic therapy (mannitol or hypertonic saline), external ventricular drainage, decompressive hemicraniectomy (DHC), and duroplasty or strokectomy may be necessary. Chapter 63, Traumatic Brain injury and Elevated Intracranial Pressure, offers further details on the use of osmotic therapy. Algorithm 55.1 demonstrates a stepwise approach to managing patients with stroke complicated by cerebral edema.

ALGORITHM 55.1 Management of Malignant Cerebral Edema Due to Stroke

Stage 1: Initial intensive care and monitoring

- Monitoring of vital signs and mental status at least every 2 h
- Keep the head of bed elevated at 30°.
- Avoid jugular compression by keeping head midline.
- Maintain normothermia and euglycemia.
- Avoid hypotonic solutions.
- Permissive hypertension, treat only SBP >220 mm Hg or DBP >120 mm Hg
- Intubation for airway protection (GCS <9 or bulbar weakness)

↓

Stage 2: Osmotic therapy for intracranial hypertension

- Avoid hypercarbia (ascertain adequate minute ventilation, treat fever).
- Give intravenous boluses of mannitol (see Chapter 63).
- Consider hypertonic saline if mannitol is unsuccessful or contraindicated.

↓

Stage 3: Surgery for cerebral edema—Consult neurosurgeon for possible decompressive hemicraniectomy +/– strokectomy

- Allow surgical evaluation *before* offering to family
- Continue osmotic therapy and medical management.

↓

Stage 4: Other interventions

- Induced hypothermia
- Deep sedation

ABBREVIATIONS

DBP: diastolic blood pressure
GCS: Glasgow Coma Scale Score
SBP: systolic blood pressure

While several trials have confirmed a significant survival benefit of DHC in large hemispheric strokes when performed within 48 hours from ictus, the effect of DHC on functional outcome, however, was not significantly improved; patients who would have died without surgical intervention ended up with severe disability, dependent on others for care. Therefore, as with all major interventions, one must establish a clear understanding of the patient's and family's wishes regarding goals of care and the degree of interventions desired for treating malignant cerebral edema.

Cerebellar infarction causing brainstem compression and obstructive hydrocephalus should be treated with decompressive suboccipital craniectomy and CSF diversion via ventriculostomy.

A brief period of hyperventilation for acutely decompensating patients with edema and evidence of herniation should be considered as a transition to more definitive therapeutic interventions, like surgery or CSF diversion.

SEIZURES

Seizure prophylaxis is not indicated in ischemic stroke; in fact, some agents have been shown to worsen outcomes (ie, phenytoin, valproic acid). However, suspicion of seizure should be evaluated with electroencephalography (EEG) and be treated similarly to seizures associated with other acute neurologic conditions.

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56 Aneurysmal Subarachnoid Hemorrhage

Rajat Dhar

Subarachnoid hemorrhage (SAH) is an acute cerebrovascular disorder with bleeding into the subarachnoid space (which contains cerebrospinal fluid [CSF]), surrounding the brain and spinal cord. The most common etiology of SAH is the rupture of an intracranial aneurysm, although other etiologies may be responsible (Table 56.1). About 10% to 20% remain cryptogenic after angiographic evaluation—many of these have a *perimesencephalic* pattern of bleeding (ie, localized around the brainstem without extension into the lateral Sylvian fissures, ventricles, or brain parenchyma). This form of SAH is more benign and likely has a venous origin. Although SAH comprises only 10% of all cerebrovascular events, it affects a younger population and carries a significant mortality (20%-30% within 30 days) as well as persistent neurologic disability (both due to the initial bleed and effects of delayed ischemia). Risk factors for aneurysmal rupture include hypertension, cigarette smoking, heavy alcohol use, polycystic kidney disease, and a history of aneurysms/SAH in first-degree relatives. Patients with SAH should ideally be managed in centers with expertise in both neurocritical care and endovascular/surgical management of intracranial aneurysms (Algorithm 56.1).

ALGORITHM 56.1 **Initial Evaluation and Management of Patients With Subarachnoid Hemorrhage**

Patient has subarachnoid hemorrhage

- Presents with sudden onset of the worst headache of their life ± LOC
- Noncontrast head CT shows hyperdensity (blood) in the basal cisterns, Sylvian fissure and sulci of the brain; blood may also be present in the ventricles.
- Lumbar puncture shows xanthochromia in a patient with negative head CT.

↓

- Admission to ICU, preferably specialized neuro-ICU if available
- Bed rest, airway protection, maintain normotension (MAP <110 ± SBP <140 mm Hg), consider antifibrinolytic agent if delay to treatment, frequent neurologic examinations
- ECG, troponin, evaluate cardiorespiratory status, consider echocardiography
- Institute anticonvulsant prophylaxis, laxatives, analgesia
- Order **cerebral angiography.**
- Place EVD if signs of hydrocephalus (drowsiness, large ventricles on head CT).

↓

Aneurysm or other vascular malformation found

No →

- Consider digital subtraction angiography if initially used CTA or MRA.
- Consider other cause (trauma, PMSAH).
- Repeat angiography in 1-3 wk.

Yes ↓

Treat aneurysm/vascular malformation to prevent rebleeding

- Consult neurosurgery/neurointerventionalist to determine treatment plan (clipping vs coiling of aneurysms, embolization vs resection of AVM).
- Treatment of aneurysms within 24 h is strongly recommended.
- Evacuation of parenchymal hematoma if exam consistent with herniation/increased ICP

↓

Aneurysm "protected" (clipped or coiled successfully)

↓

Initial preventative measures for vasospasm/DCI

- Maintain euvolemia (monitoring of ins and outs, isotonic IV fluids).
- Permissive hypertension (hold antihypertensives)
- Nimodipine 60 mg orally or enterally every 4 h

Monitor closely for complications

- Frequent neurologic examinations
- EEG monitoring if reduced or fluctuating level of consciousness
- Frequent monitoring of vitals, heart rhythm, electrolytes

- Frequent monitoring of vitals, heart rhythm, electrolytes
- Monitoring of ICP, if appropriate
- Screening for vasospasm/DCI (see Algorithm 56.2)

ABBREVIATIONS

AVM:	arteriovenous malformation	ICU:	intensive care unit
CT:	computed tomography	IV:	intravenous
CTA:	CT angiography	LOC:	loss of consciousness
DCI:	delayed cerebral ischemia	MAP:	mean arterial pressure
ECG:	electrocardiography	MRA:	magnetic resonance angiography
EEG:	electroencephalography	PMSAH:	perimesencephalic subarachnoid hemorrhage
EVD:	external ventricular drain	SBP:	systolic blood pressure
ICP:	intracranial pressure		

TABLE 56.1 Cause of Subarachnoid Hemorrhage

Etiology	Clues/Comments
Intracranial aneurysm	Most common cause of spontaneous SAH, usually presents with "thunderclap headache," diffuse hemorrhage on imaging
Arteriovenous malformation	Often associated with intraparenchymal bleeding
Trauma	Blood usually more focal, located around cerebral convexity and associated with parenchymal contusions
Perimesencephalic	Angiogram negative, blood confined to cisterns around brainstem
Arterial dissection	Only if dissection extends intracranially
Coagulopathy	May be focal (with minor trauma) or diffuse, angiogram negative
Venous thrombosis	Often associated with edema and parenchymal hemorrhage
Pituitary apoplexy	Sudden headache with visual complaints and ophthalmoplegia

Etiology	Clues/Comments
Reversible cerebral vasoconstriction syndrome	Focal SAH, often at convexity Angiogram reveals diffuse segmental vasoconstriction Associated with certain medications, postpartum state, drug abuse
Pseudosubarachnoid hemorrhage	Hyperdensity within the subarachnoid space due to diffuse cerebral edema (no bleeding present); seen in hypoxic-ischemic injury, meningitis, etc

SAH, subarachnoid hemorrhage.

Diagnosis and Initial Management

Patients with SAH usually present with sudden severe headache that reaches maximum intensity within seconds (ie, thunderclap headache). This may be associated with transient loss of consciousness (ie, syncope) or persistent alteration in level of consciousness, including coma. Meningismus develops often over hours. The diagnosis is confirmed by noncontrast computed tomography (CT) of the head that has almost perfect (99%) sensitivity if performed within 24 hours of symptom onset. Those presenting in a delayed state (ie, headache for >24 hours) or with negative CT despite clinical suspicion should undergo lumbar puncture to evaluate for red blood cells and *xanthochromia* (the yellow discoloration of centrifuged CSF seen with blood breakdown) as delay or misdiagnosis of SAH places them at risk for aneurysmal rebleeding and worse outcome. Magnetic resonance imaging (MRI) is another consideration for those with thunderclap headache and delayed presentation; it may reveal subacute bleeding within the subarachnoid spaces missed by CT. Those with confirmed SAH but negative initial angiography should undergo repeat angiography (or CT angiography) in 1 to 3 weeks to exclude a missed aneurysm (especially if the bleeding is diffuse and not just localized in a perimesencephalic pattern).

Acute hydrocephalus from obstruction to CSF flow, manifested by enlargement of the lateral ventricles (especially temporal horns) on CT, is seen in approximately half of patients and may lead to impaired mental status, requiring urgent ventriculostomy to divert CSF. Once the patient has been diagnosed and stabilized, cerebral angiography should be performed to evaluate for an aneurysm or other vascular lesion. Conventional catheter angiography remains the gold standard but CT angiography may be used as an initial screening test, although it may miss small aneurysms. The clinical severity of SAH is graded using either the Hunt and Hess or World Federation of Neurosurgical Societies' scales (Table 56.2). Survival is inversely proportional to grade, with grade V patients who do not improve with initial stabilization (including ventriculostomy to drain CSF if hydrocephalus is present) almost invariably doing poorly. The amount of blood on admission CT scan is graded using the modified Fisher scale (Table 56.3); higher grade patients are at greater risk for vasospasm, delayed ischemic deficits, and strokes, mandating closer monitoring.

TABLE 56.2 Clinical Grading Scales

Grade	Criteria
Hunt and Hess Grading System	
1	Asymptomatic or mild headache
2	Moderate-to-severe headache, nuchal rigidity, or cranial nerve palsy
3	Confusion, lethargy, and/or mild focal neurologic deficit
4	Stupor and/or hemiparesis
5	Comatose, posturing
World Federation of Neurosurgical Societies' Scale	

Grade	Criteria
I	GCS 15, no motor deficit
II	GCS 13-14, no motor deficit
III	GCS 13-14 or motor deficit
IV	GCS 7-12
V	GCS 3-6

GCS, Glasgow Coma Scale.

The risk of rebleeding is as high as 20% in the first 24 to 48 hours after SAH and is the most common cause of early death (along with ventricular arrhythmias). Early treatment of the ruptured aneurysm is critical to prevent rebleeding and may be accomplished by surgical clipping (with craniotomy) or through endovascular approaches such as coiling. The patient's age, clinical condition, and anatomy/location of the aneurysm will inform the preferred treatment, in which is determined through discussion between the neurosurgeon and endovascular specialist. Prior to definitive aneurysmal treatment, blood pressure should be controlled to prevent further bleeding; mean arterial pressure (MAP) should be kept below 110 mm Hg and/or systolic blood pressure below 140 mm Hg. Short-acting antihypertensives (eg, labetalol, nicardipine), analgesics, and sedatives are preferred. Blood pressure can be liberalized after successful securing of the aneurysm. Administration of antifibrinolytic agents such as tranexamic acid (1 g IV every 4-6 hours, prior to aneurysm treatment) may reduce the risk of rebleeding but have not demonstrated improved outcomes; they may be given when there will be a significant delay from SAH diagnosis to aneurysm treatment.

Aneurysmal rupture triggers a molecular cascade culminating in the release of catecholamines and cytokines. This sympathetic hyperactivity may induce cardiopulmonary dysfunction. Electrocardiography (ECG) changes are common and troponin

levels are mildly elevated in 20% to 30%. Ten percent of patients (especially those with severe SAH and elevated cardiac enzymes) will have stunned myocardium with wall-motion abnormalities or globally depressed systolic function on echocardiography. A takotsubo pattern of apical akinesis and ballooning is one typical echocardiographic pattern seen. Coronary angiography is not necessary in most and is invariably unrevealing (ie, no obstructive lesion). This form of “stress-induced cardiomyopathy” is reversible and usually resolves within 1 to 2 weeks; some patients will require inotropic support in the acute period. Pulmonary edema and hypoxemia are seen in 10% to 20% and may have both cardiogenic as well as neurogenic origins.

Aneurysm rupture and the neuroinflammatory cascade triggered in its aftermath can also lead to acute neurologic consequences, termed *early brain injury*. Some patients develop diffuse brain swelling resulting in global cerebral edema. This may be associated with elevations in intracranial pressure and neurologic deterioration in the first few days after SAH.

Complications of Subarachnoid Hemorrhage

Seizures most often occur early after SAH (either at ictus or prior to hospitalization in 5%-10%). However, there is an approximately 5% risk of seizures in-hospital and, despite lack of evidence for their benefit, time-limited anticonvulsant prophylaxis is often provided for patients after SAH. This can either be just for the immediate perioperative period (eg, 3-day course) or continued until hospital discharge in high-risk patients (eg, with parenchymal hematoma) or those having seizures after admission. Levetiracetam at a dose of 1,000 mg twice daily is one commonly used regimen. Those remaining or becoming poorly responsive after SAH or who have fluctuating neurologic examinations should undergo electroencephalography (EEG) monitoring to exclude subclinical seizures.

Hyponatremia occurs in 30%, most often 4 to 10 days after admission. There may be components of the syndrome of inappropriate antidiuretic hormone secretion (SIADH, euvolemic) and cerebral salt wasting (CSW, hypovolemic). Distinguishing between the two is important (but often challenging) as therapeutic strategies are different: avoiding excess water intake with SIADH versus replacing volume in CSW. Total fluid restriction should never be utilized for hyponatremia after SAH (even if SIADH is suspected) as hypovolemia has been shown to elevate the risk of cerebral infarction. As SIADH and CSW often overlap, it is advisable to assess volume status, and unless hypovolemia can be confidently excluded, then saline replacement (either with normal or hypertonic saline infusions) is the safer approach. This can be accompanied by oral fluid restriction of 1 to 1.5 L/d. All patients with SAH should have daily measurements of serum sodium as well as close monitoring of fluid balance. They should not receive hypotonic fluids, and diuretics should be restricted as hypovolemia promotes cerebral ischemia. Central fever is also commonly seen and may be part of a systemic inflammatory response (SIRS) making true infection difficult to differentiate and diagnose in these patients.

Cerebral Vasospasm and Delayed Cerebral Ischemia

Cerebral infarction as a result of delayed ischemia is the major source of secondary disability after SAH. Arterial narrowing (ie, vasospasm) is seen on angiography in a majority of patients with SAH between 4 and 21 days after bleeding (peaking around days 7-10) and is more likely in those with greater thickness of SAH and intraventricular hemorrhage (estimated by the modified Fisher scale, Table 56.3). Some patients with vasospasm will remain asymptomatic, but others will develop neurologic deficits related to reductions in cerebral blood flow (CBF) below ischemic thresholds. This reduction in CBF and oxygen delivery may be worsened by

hypovolemia, hypotension, and anemia. For this reason, patients with SAH should be kept euvolemic by adjustment of intravenous fluids and normotensive (avoiding blood pressure [BP]-lowering medications). The optimal hemoglobin and role of transfusion are less clear. All patients should receive nimodipine, a calcium channel antagonist that has demonstrated efficacy in improving neurologic outcomes (at a dose of 60 mg every 4 hours enterally, continued for 21 days). The dose may be halved and given every 2 hours if blood pressure drops after each dose. Some centers employ transcranial Doppler (TCD) to screen for vasospasm, as an increase in velocities in the basal cerebral vessels suggests a decrease in their caliber. Prophylactic hypervolemia or hypertensive therapy is not effective in either improving cerebral perfusion or preventing deficits from vasospasm.

TABLE 56.3 CT Grading Scale for Risk of Vasospasm

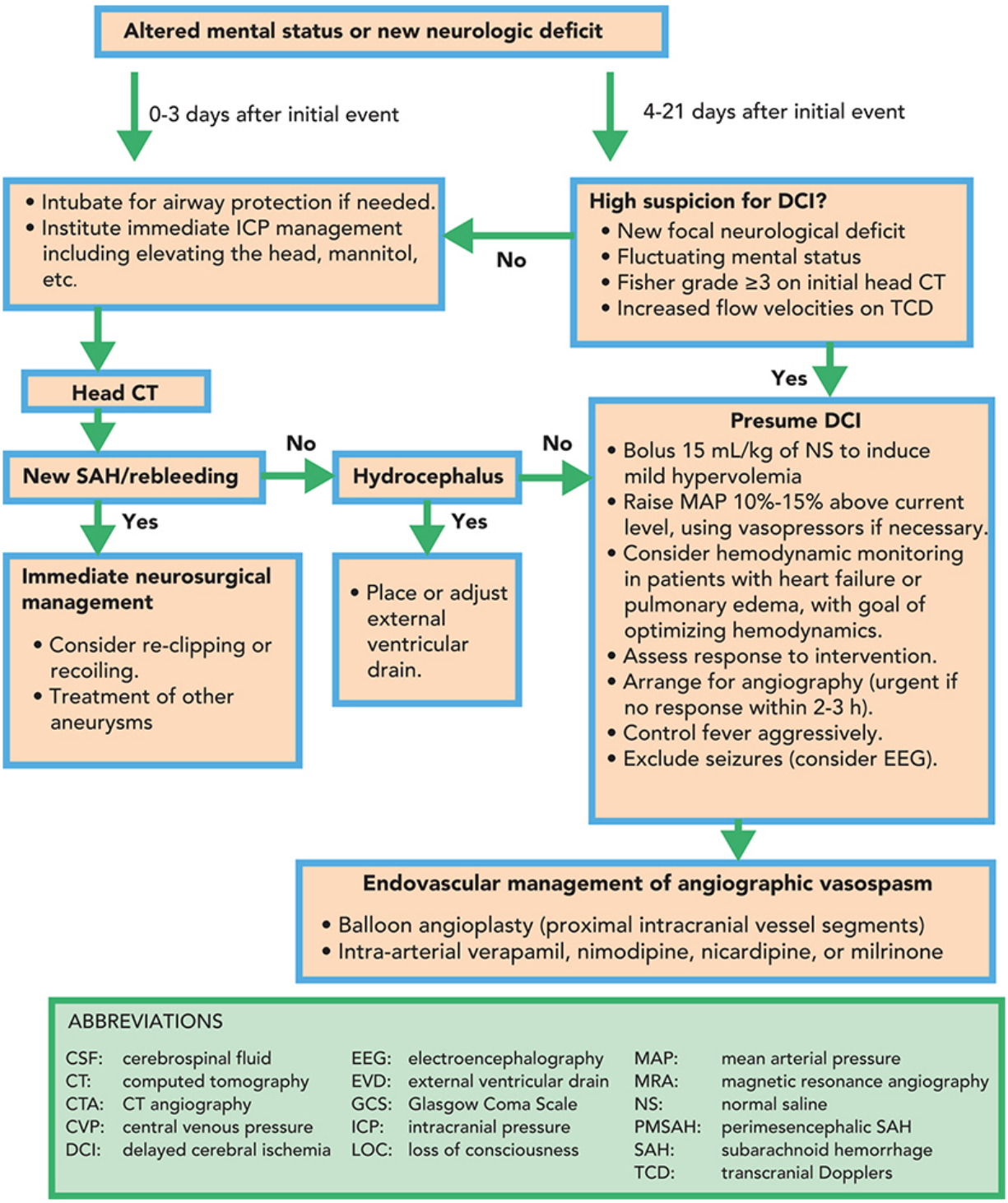
Amount of SAH in Basal Cisterns	IVH	Modified Fisher Grade
Diffuse or localized, thick	Present	4
Diffuse or localized, thick	Absent	3
Diffuse or localized, only thin SAH	Present	2
Only thin SAH	Absent	1
No SAH	Present	2
No SAH	Absent	0

SAH is considered thick if it completely fills at least one cistern or fissure. IVH is considered present if there is blood in both lateral ventricles.
CT, computed tomography; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

Any alteration in neurologic status (ie, new or worsening of neurologic deficits or persistent alteration in mentation) after SAH

requires prompt evaluation for ischemia (Algorithm 56.2). Confounders should be excluded, usually with head CT to rule out hydrocephalus, new bleeding, or cerebral edema. Metabolic derangements including hyponatremia, fever, hypoxemia or hypercapnia, and seizures can also cause neurologic worsening and should be excluded. If ischemia remains suspected, then hemodynamic augmentation to raise cerebral perfusion should be initiated. The so-called "Triple-H" therapy (hypervolemia, hypertension, hemodilution) is instituted with a fluid bolus and vasopressors titrated to raise MAP by 10% to 15% above the patient's baseline. Hemodilution is generally avoided unless polycythemia is present. In cases of cardiac failure, inotropic support may be helpful in reversing neurologic deficits. Noninvasive cardiac monitoring may be helpful to optimizing hemodynamics. Patients with suspected delayed cerebral ischemia should undergo angiography to evaluate for vasospasm (further confirming the clinical diagnosis). While CT angiography (sometimes with CT perfusion) is a reasonable initial screen for vasospasm and hypoperfusion, conventional angiography allows endovascular therapies to be administered, including intra-arterial injections of vasodilators (eg, verapamil, nimodipine, nicardipine, milrinone) and balloon angioplasty of accessible proximal arterial segments. While vasodilators usually only offer transient relief of arterial narrowing, angioplasty more durably reverses vasospasm and can improve neurologic deficits. In contrast, vasospasm in the absence of neurologic deficits (ie, in those remaining asymptomatic) should generally not be treated, but close monitoring continued for a few more days with maintenance of euvolemia and permissive hypertension.

ALGORITHM 56.2 **Evaluation and Management of Complications After Subarachnoid Hemorrhage**


Altered mental status or new neurologic deficit
0-3 days after initial event
4-21 days after initial event
• Intubate for airway protection if needed.
• Institute immediate ICP management including elevating the head, mannitol, etc.
No
High suspicion for DCI?
• New focal neurological deficit
• Fluctuating mental status
• Fisher grade ≥3 on initial head CT
• Increased flow velocities on TCD
Yes
Head CT
No
No
New SAH/rebleeding
Hydrocephalus
Presume DCI
• Bolus 15 mL/kg of NS to induce mild hypervolemia
• Raise MAP 10%-15% above current level, using vasopressors if necessary.
• Consider hemodynamic monitoring in patients with heart failure or pulmonary edema, with goal of optimizing hemodynamics.
• Assess response to intervention.
• Arrange for angiography (urgent if no response within 2-3 h).
• Control fever aggressively.
• Exclude seizures (consider EEG).
Yes
Yes
Immediate neurosurgical management
• Consider re-clipping or recoiling.
• Treatment of other aneurysms
• Place or adjust external ventricular drain.
Endovascular management of angiographic vasospasm
• Balloon angioplasty (proximal intracranial vessel segments)
• Intra-arterial verapamil, nimodipine, nicardipine, or milrinone
ABBREVIATIONS
CSF: cerebrospinal fluid
CT: computed tomography
CTA: CT angiography
CVP: central venous pressure
DCI: delayed cerebral ischemia
EEG: electroencephalography
EVD: external ventricular drain
GCS: Glasgow Coma Scale
ICP: intracranial pressure
LOC: loss of consciousness
MAP: mean arterial pressure
MRA: magnetic resonance angiography
NS: normal saline
PMSAH: perimesencephalic SAH
SAH: subarachnoid hemorrhage
TCD: transcranial Dopplers

Hemodynamic augmentation should be titrated to clinical effect (ie, reversal of new/worsening deficits) rather than a specific blood pressure target, although avoiding MAP targets above 130 to 140 mm Hg may prevent iatrogenic posterior reversible encephalopathy

syndrome (PRES). High doses of vasopressors may be required for induced hypertension. Intravenous milrinone can be used as an alternative or adjunct to vasopressors in refractory cases or in those with impaired cardiac function. Close observation for complications from hemodynamic therapy (eg, pulmonary edema, arrhythmias, cardiac injury, worsening cerebral edema or hemorrhagic transformation of an established infarct, hypertensive encephalopathy) is mandatory. Once clinical response is achieved, this goal blood pressure should be maintained for at least 48 to 72 hours before cautious and gradual weaning of vasopressors/inotropes and blood pressure targets is attempted. Improvement on a repeat angiogram may be helpful in guiding when to wean therapy in more complex cases.

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57 Intracerebral Hemorrhage

Ramiro G. Castro-Apolo and Salah G. Keyrouz

Intracerebral hemorrhage (ICH) is a focal collection of blood within the brain parenchyma with potential extension into adjacent brain compartments (ventricles, subarachnoid, and/or subdural spaces). According to the latest Nationwide Inpatient Sample and US Census Bureau data, the annual US incidence of ICH is 23.15 per 100,000. An 11% increase during the last 15 years coincided with higher prevalence of hypertension and anticoagulation use among patients hospitalized with ICH. It is the second most common stroke subtype accounting for 10% to 15% of all strokes with a higher proportion in the African American and Asian population. The case fatality rate reaches 40% at 1 month and 54% at 1 year. Only 27% of patients achieve functional independence at 3 months.

ICH is a heterogeneous group of conditions and can be divided into primary and secondary ICH (Table 57.1). The two most common causes of ICH are hypertension and cerebral amyloid angiopathy (CAA). Chronic arterial hypertension leads to a vasculopathy (lipohyalinosis), involving small branching vessels such as lenticulostriate, thalamic, and pontine perforating arteries. Therefore, hypertensive hemorrhages are usually found in the deep gray matter (basal ganglia and thalamus), pons, or cerebellum (Figure 57.1). CAA results from deposition of amyloid-beta peptide in the walls of small- to medium-sized leptomeningeal and cortical vessels. It typically affects older individuals and leads to cortical-subcortical (lobar) hemorrhages. Anticoagulation increases the risk and severity of ICH and rebleeding in any of these settings.

TABLE 57.1 Etiologies of Intracranial Hemorrhage

Primary ICH	Clues to the Etiology	Imaging Findings
Hypertension	History and stigmata of hypertension	Typical locations: Basal ganglia (55%), thalamus (26%), cerebral hemispheres (11%), pons (8%), cerebellum (7%)
Cerebral amyloid angiopathy (CAA)	Older age, history of cognitive impairment, prior transient focal neurologic episodes (TFNEs) or ICH	Superficial, lobar distribution; lobulated appearance, rupture into subarachnoid or subdural spaces, secondary IVH; more frequent in temporal and occipital regions; less common in cerebellum; spares deep hemispheric structures and brainstem; “microbleeds” or superficial siderosis on MRI (gradient echo, T2*-weighted sequences)
Sympathomimetic drug use, for example • Cocaine • Methamphetamine • Pseudoephedrine	Younger age, history of drug use	More frequent subcortical pattern and IVH. Similar to hypertensive ICH
Coagulopathy	History of anticoagulant use	Lobulated, fluid-fluid levels within hematoma
Secondary ICH		
Vascular malformations • Arteriovenous malformations • Cavernous malformations • Saccular aneurysm • Mycotic aneurysm	Younger patients (<45 y), normotensive, family history, prior seizure, or hemorrhage in same brain region	Vascular imaging (CTA, MRA, or DSA) with typical findings

Primary ICH	Clues to the Etiology	Imaging Findings
Dural arteriovenous fistula		
Moyamoya	African American, Asian, sickle cell disease	Puff of smoke on DSA. Might also result in cerebral infarcts, IVH, or SAH
Hemorrhagic conversion of ischemic stroke	Prior ischemic stroke	Petechial hemorrhages, patchy, scattered throughout the infarcted tissue. An outline of the infarct could be delineated on CT.
Cerebral venous sinus thrombosis	Eclampsia, pregnancy Subacute headache	Noncontrast CT with hyperdensity of sinus, CT venogram, or MR venogram with filling defect in cerebral sinus
Cerebral vasculitis	Young individual, history of headaches and prior strokes	Nonspecific findings. Infarcts and white matter disease in multiple brain regions
Tumor	Known primary tumor, prior hemorrhage in same territory	Significant edema surrounding acute hemorrhage, contrast enhancement contiguous to acute hematoma

CT, computed tomography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging ; SAH, subarachnoid hemorrhage.

FIGURE 57.1 **Hypertensive ICH**. Acute left putaminal ICH; axial, noncontrasted head CT. CT, computed tomography; ICH, intracerebral hemorrhage.

Clinical Presentation

The presenting symptoms of ICH are nonspecific and include the tetrad of headache, altered level of consciousness, nausea/vomiting, and focal neurologic symptoms according to the anatomic location of hematoma. Symptom onset is usually abrupt but can be insidious depending on the underlying etiology. Headaches are seen in up to 30% of patients. Nausea and vomiting are frequently observed in posterior fossa ICH due to vestibular dysfunction or hemorrhage into the fourth ventricle. Nonetheless, nausea and vomiting can also herald increased intracranial pressure (ICP) in supra-tentorial hemorrhages. The majority of patients present with depressed level of consciousness. Seizures, focal or generalized tonic/clonic, are associated with cortical involvement. Progressive clinical deterioration is common, and initial management should be done in an intensive care setting. Early hematoma growth, or rebleeding, even in the absence of a coagulopathy, affects approximately one-third of patients and is mostly observed within the first 6 hours but can be seen up to 24 hours after onset. Hematoma growth is associated with clinical deterioration and worse outcomes.

Brain injury due to ICH is mediated through several mechanisms. They include hematoma growth that dissects neuronal pathways and brain tissue, ICP elevation due to mass effect resulting in adjacent damage and/or brain tissue herniation, and highly toxic blood degradation products leading to cerebral edema, seizures, fever, and autonomic changes.

Diagnosis

Patients with suspected intracranial hemorrhage should receive an expedited neurologic assessment and workup. A brief medical history should be obtained, focusing on anticoagulant use, recent head trauma, illicit drug use, and any history of hypertension or prior hemorrhagic or ischemic stroke. Noncontrast head computed

tomography (CT) is the most rapid and readily available tool to establish the diagnosis of ICH. Within the first week, CT has a high sensitivity (89%) and specificity (100%) for acute ICH. It allows for the anatomic localization of hematoma, diagnose possible intraventricular extension, and could possibly identify an underlying etiology. It also provides ground to estimating hematoma volume. A "spot sign," visualized with the addition of contrast, represents active contrast extravasation into the hematoma and has been associated with expansion in 60% of patients (Figure 57.2). A CT-angiogram performed with contrast during the acute phase has an overall sensitivity of 97% and specificity of 98.9% for causal vascular abnormalities, compared with digital subtraction angiography (DSA) as a gold standard (Algorithm 57.1).

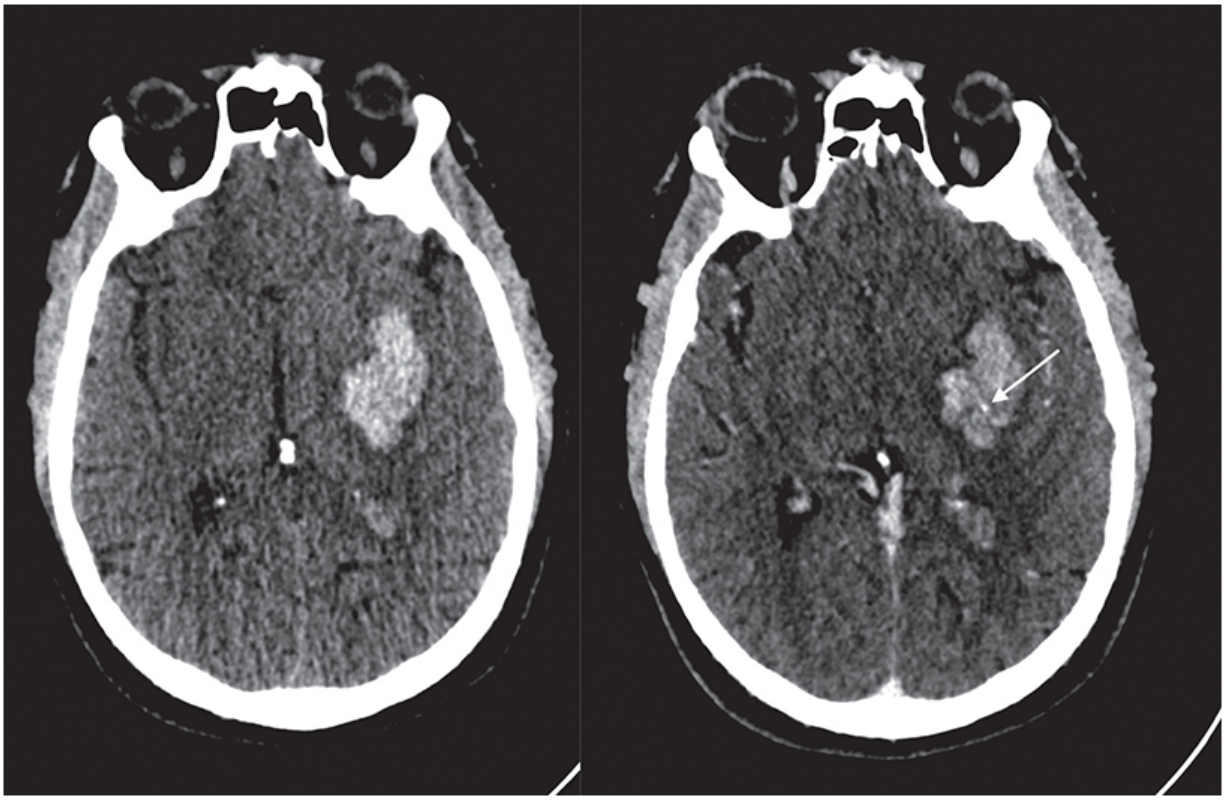
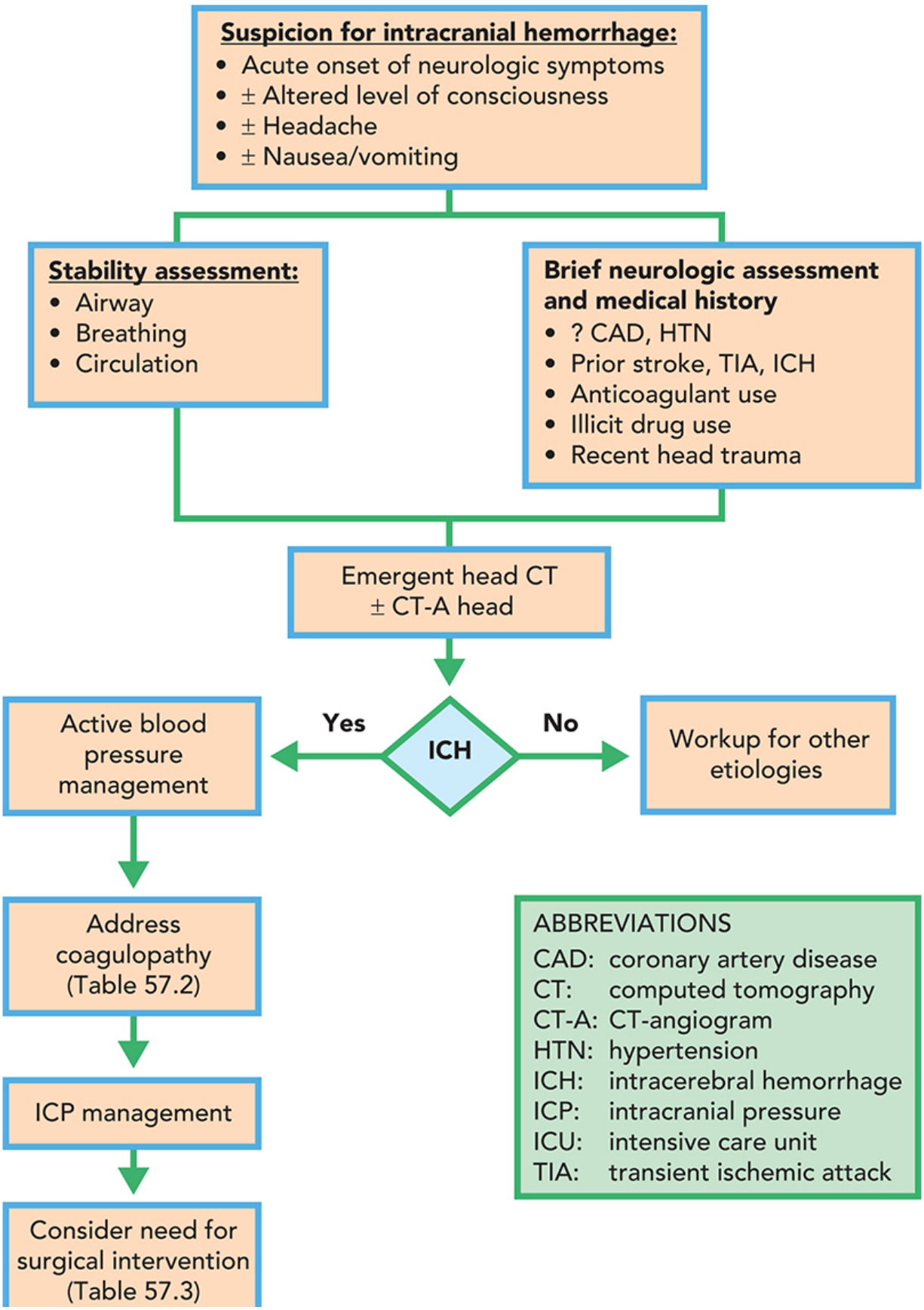
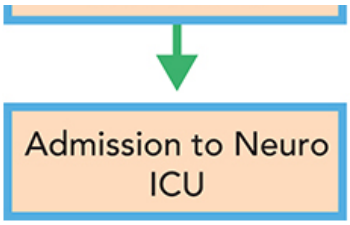


FIGURE 57.2 **Left hypertensive putaminal hemorrhage**. Spot sign (arrow) following contrast administration.

ALGORITHM 57.1 Approach to the Patient With Suspected ICH


Suspicion for intracranial hemorrhage:
• Acute onset of neurologic symptoms
• ± Altered level of consciousness
• ± Headache
• ± Nausea/vomiting
Stability assessment:
• Airway
• Breathing
• Circulation
Brief neurologic assessment and medical history
• ? CAD, HTN
• Prior stroke, TIA, ICH
• Anticoagulant use
• Illicit drug use
• Recent head trauma
Emergent head CT ± CT-A head
ICH
Yes
No
Active blood pressure management
Workup for other etiologies
Address coagulopathy (Table 57.2)
ICP management
Consider need for surgical intervention (Table 57.3)
ABBREVIATIONS
CAD: coronary artery disease
CT: computed tomography
CT-A: CT-angiogram
HTN: hypertension
ICH: intracerebral hemorrhage
ICP: intracranial pressure
ICU: intensive care unit
TIA: transient ischemic attack



Management

A patient with suspected ICH constitutes a neurologic emergency, and due to a significant risk for early deterioration and cardiorespiratory compromise, should be medically stabilized in an expedited fashion before diagnostic imaging is obtained.

AIRWAY

The initial management includes a brief assessment of the patient's ability to protect their airway. In a setting of impaired arousal with concomitant risk of aspiration, hypoxemia, or hypercarbia, rapid sequence intubation should be undertaken and ventilator support initiated. Given concerns for transient elevations of ICP during laryngoscopy and associated worsening of mass effect, induction agents should be chosen that minimize side effects. Pretreatment with lidocaine (1.5 mg/kg) 2 to 3 minutes prior to intubation is felt to mitigate the rise in ICP. Etomidate is thought to have the least impact on blood pressure (BP) and is a preferred induction agent barring any contraindications.

BLOOD PRESSURE MANAGEMENT

Extreme elevation in BP in the immediate period after ICH is thought to increase the risk of early neurologic deterioration and contribute to hematoma expansion. However, robust scientific evidence proving reduced incidence of hematoma expansion with aggressive BP reduction is lacking. The current recommendations are based on data from two large trials (INTERACT-2 [Intensive Blood Pressure

Reduction in Acute Cerebral Hemorrhage Trial 2] and ATACH-2 [Antihypertensive Treatment of Acute Cerebral Hemorrhage 2]). Evidence suggests that lowering systolic BP (SBP) to a target of 140 mm Hg is safe but not associated with improved functional outcome in patients presenting with acute, mild-to-moderate severity ICH and SBP between 150 and 220 mm Hg. Acute lowering of SBP below 140 mm Hg is potentially harmful and should be avoided. Commonly used antihypertensive drugs are short-acting and titrated rapidly, for example intravenous beta blockers or calcium channel blockers. Nitrates are avoided because of the risk of cerebral vasodilatation causing worsening edema. Addressing pain may also help to control elevated BP.

COAGULOPATHY

All anticoagulants and antiplatelet agents should be stopped immediately. Existing guidelines emphasize the rapid correction of coagulopathy in patients with intracranial hemorrhage (Table 57.2).

TABLE 57.2 Stabilizing Coagulation Status After Intracerebral Hemorrhage

- Discontinue all antiplatelet and anticoagulant medications.
- Reverse anticoagulation or correct coagulopathy:
  - Warfarin: Vitamin K 10 mg IV or enterally daily for 3 d
  - Prothrombin complex concentrate (PCC) for urgent surgical procedure (or if risk for volume overload from fresh frozen plasma):
    - INR 2-3.9: 25 units/kg (max. 2,500 units)
    - INR 4-6: 35 units/kg (max. 3,500 units)
    - INR >6: 50 units/kg (max. 5,000 units)
  - Fresh frozen plasma 15-20 mL/kg
- Platelet and coagulation factor replacement as needed for thrombocytopenia and coagulation factor deficiency, respectively
- LMWH (last dose < 8 h ago): Protamine 1 mg/100 anti-Xa units (max. 50 mg)
- Dabigatran: Idarucizumab 5 g once

- Apixaban and rivaroxaban:
  - Consider activated charcoal if last dose less than 2 h.
- Andexanet alfa:
  - Low dose (400 mg IV bolus and 2 h infusion 4 mg/min) if administration >8 h from last dose
  - High dose (800 mg IV bolus and 2 h infusion 8 mg/min) if administration <8 h from last dose
  - Consider PCC 50 units/kg (max. 5,000 units) as alternative agent.
- Follow coagulation panel frequently, keep corrected for 24-48 h.

INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin.

Options for correction of warfarin-induced coagulopathy include fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC). If available, PCC are generally preferred over FFP. They can be administered more rapidly, correct the coagulopathy faster, and require less volume of infusion. Patients using warfarin should in addition receive vitamin K. Andexanet alfa, a specific reversal agent, can be used in patients with direct Xa inhibitor-associated ICH (rivaroxaban, apixaban, and edoxaban), though its superiority over PCC is yet to be established. A monoclonal antibody, idarucizumab, is available for the rapid and reliable reversal of dabigatran. For patients with spontaneous ICH on antiplatelet agents and who require emergent neurosurgical interventions, platelet transfusion might be considered to reduce postoperative bleeding and mortality. Platelet transfusion outside of this setting or in the absence of thrombocytopenia has been associated with increased mortality and should be avoided.

VENTRICULOSTOMY AND INTRACRANIAL PRESSURE MANAGEMENT

Hydrocephalus complicates up to 50% of ICH cases and is associated with younger age, lower Glasgow Coma Scale (GCS) score, deep hemorrhages, intubation, and mortality. In patients with decreased level of consciousness (GCS score ≤8), clinical evidence

of cerebral herniation, or those with significant intraventricular hemorrhage (IVH) or hydrocephalus, monitoring of ICP with a ventricular catheter should be considered. ICP greater than 20 mm Hg was seen in 70% of patients in one retrospective study and was most common in young patients with supratentorial hemorrhage. Increased ICP can be treated with hyperosmolar agents, for example mannitol or hypertonic saline, cerebrospinal fluid diversion via ventriculostomy, sedation, or therapeutic hypothermia (see ICP treatment Algorithm 63.1 in Chapter 63).

SEIZURES

The primary neuronal damage and blood degradation products increase seizure risk after ICH. Seizures occur in 5% to 15% of patients, usually in the first few days of hospitalization. Seizure prophylaxis is not indicated in ICH management because available evidence has failed to show improvement of functional outcomes, long-term seizure control, or lower mortality. Continuous electroencephalography should be considered in patients with depressed mental status out of proportion to the degree of brain injury or fluctuation in neurologic examination. Patients with clinical seizures and those with mental status changes and electrographic seizures should be treated with anticonvulsant drugs.

NEUROSURGICAL INTERVENTION

In patients with cerebellar hemorrhage who are deteriorating neurologically or who have clinical evidence of brainstem compression and/or hydrocephalus from ventricular obstruction, surgical evacuation of hemorrhage is recommended as soon as possible (Table 57.3). Surgical management in patients with supratentorial hemorrhage (Figure 57.3) remains controversial due to lack of good evidence. More recently, minimally invasive surgery (MIS) has shown promising results; however, the exact nature of the benefit often varies between studies. MIS for supratentorial ICH has the appeal of relieving pressure from hematoma, reducing

perihematomal edema, and, compared with conventional craniotomy, minimizing disruption of healthy brain tissue. As a result, MIS with endoscopic or stereotactic aspiration, with or without thrombolytic use, appears to be safe and may reduce mortality. Although it may also improve functional outcomes, the level of evidence is weaker. The 2022 American Heart Association (AHA) guidelines for ICH management supports the use of MIS over conventional craniotomy with evacuation.

TABLE 57.3 Indications for Neurosurgical Intervention After ICH

- Posterior fossa or temporal lobe hemorrhage >3 cm
- ICH causing hydrocephalus or brainstem compression
- Hydrocephalus or IVH requiring EVD
- Complicated cases requiring ICP monitoring

EVD, external ventricular drain; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IVH, intraventricular hemorrhage.

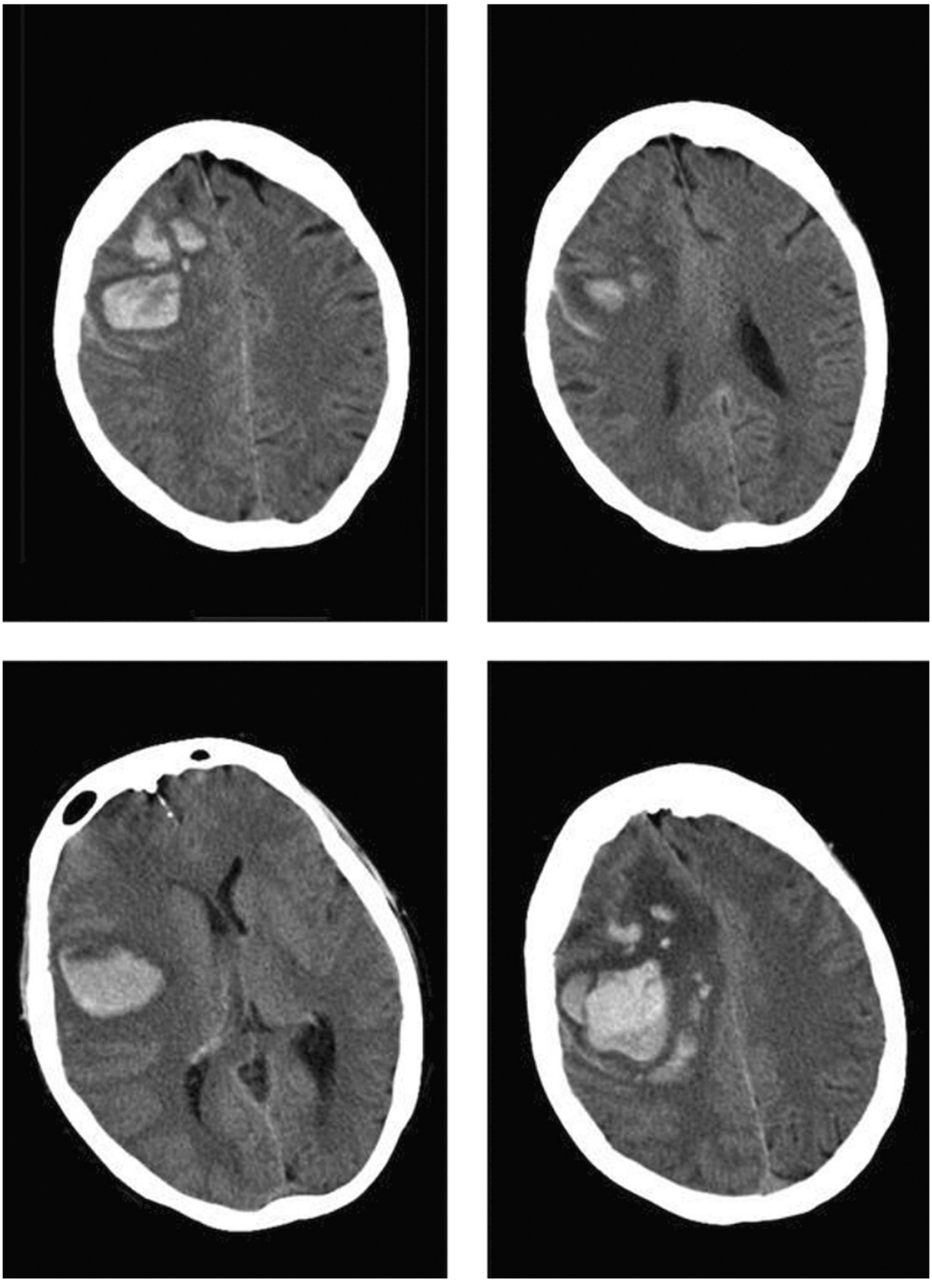


FIGURE 57.3 **CAA-related intracranial hemorrhage**. Lobar hemorrhage due to cerebral amyloid angiopathy. **Top panel:** Admission noncontrasted, axial head CT. **Bottom panel:** Axial, noncontrasted head CT 4.5 hours later. CAA, cerebral amyloid angiopathy; CT, computed tomography.

FEVER

Fever after ICH is common and should be treated aggressively given an independent association with poor outcome. Sustained temperature elevations greater than 38.5 °C should be treated with acetaminophen, chilled saline infusions, and cooling blankets. Concurrently, a thorough search for a potential source of infection should be undertaken. In the case of medically refractory fever, consideration should be made to initiate surface, esophageal, or endovascular cooling with heat exchange catheters. Fever of central origin is a diagnosis of exclusions but can be seen more frequently with intraventricular extension of hemorrhage and pontine hemorrhages.

GENERAL CARE

Patients with ICH, like all patients who are critically ill, are at risk for a myriad of complications, including myocardial infarctions, heart failure with pulmonary edema, deep vein thrombosis (DVT), aspiration pneumonia, urinary tract infections, pressure ulcers, and orthopedic complications (eg, contractures). Sequential compression devices should be used on admission, and subcutaneous low-molecular-weight or unfractionated heparin for DVT prophylaxis can be started after 48 hours if there is no evidence of hematoma expansion. Spontaneous lobar ICH in the setting of probable CAA carries a relatively high risk of recurrence, thus avoidance of long-term anticoagulation for indications such as nonvalvular atrial fibrillation in these patients is recommended. In the presence of a clear indication for anticoagulation (ie, mechanical heart valve) or antiplatelet therapy (ie, coronary artery stents), it is reasonable to restart anticoagulation in nonlobar ICH in 1 to 4 weeks and

antiplatelet therapy in all ICH, after documentation of cessation of bleeding.

Prognosis

Despite recent advances in the care of ischemic strokes with subsequent improved outcomes, ICH remains one of the acute neurologic disorders with the worst prognosis; case fatality rates reach 40% at 1 month and 54% at 1 year, and only 27% of patients achieve functional independence at 3 months. GCS score, hematoma volume, intraventricular extension, infratentorial origin, and advanced age form the basis of the ICH score—a frequently used and validated grading scale for risk stratification of patients upon presentation (Table 57.4). Hematoma volume in milliliters is reliably approximated using the *ABC*/2 method (Figure 57.4): *A* represents the largest hematoma diameter on axial head CT, *B* the largest diameter perpendicular to *A*, and *C* the approximate number of CT slices with hemorrhage multiplied by slice thickness (usually 0.3 or 0.5 cm). The total is divided by 2.

TABLE 57.4 ICH Score

ICH Score Component	Points
GCS score	
• 3-4	2
• 5-12	1
• 13-15	0
ICH volume, cm^3	

ICH Score Component	Points
• >30	1
• <30	0
Intraventricular hemorrhage	
• Yes	1
• No	0
Infratentorial origin	
• Yes	1
• No	0
Age, years	
• >80	1
• <80	0
Total ICH score (0-6):	30-d mortality:
• 0	0%
• 1	13%
• 2	26%
• 3	72%
• 4	97%
• 5	100%

GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage.

FIGURE 57.4 ***ABC*/2 formula for calculation of hematoma volume**. Estimation of hematoma volume using the *ABC/2* method (*A*, maximum diameter of hematoma on the reference axial slice with the largest area of hematoma; *B*, maximum hematoma diameter perpendicular to *A*; and *C* [not depicted], the number of slices in the vertical plane with visible hematoma multiplied by slice thickness [typically 0.3 or 0.5 cm]; the hematoma volume in milliliters is [*A* × *B* × *C* × 0.5 cm]/2).

The FUNC (Functional Outcome in Patients With Primary Intracerebral Hemorrhage) score, helps to predict functional independence at 3 months. It takes into account age, admission, GCS, ICH volume and location, and presence of premorbid cognitive impairment (Table 57.5).

TABLE 57.5 FUNC Score

Components	Points
ICH volume, cm^3	
• <30	4
• 30-60	2
• >60	0
Age, years	
• <70	2
• 70-79	1
• 80 or more	0
ICH location	
• Lobar	2

Components	Points
• Deep • Infratentorial	1 0
GCS score • 9 or more • 8 or less	2 0 1 0
Pre-ICH cognitive impairment • No • Yes	
Total FUNC score (0-11):	90-d functional independence:
• 0-4	0%
• 5-7 • 8 • 9-10 • 11	1%-20% 21%-60% 61%-80% 81%-100%

FUNC, functional outcome in patients with primary intracerebral hemorrhage; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage.

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58 Coma

Baback Arshi

Coma is an eyes closed unresponsive state. In contrast, unresponsive states with open eyes include persistent vegetative state, minimally conscious state, locked-in syndrome, abulia, and akinetic mutism. Differentiating between coma and these other diagnoses has prognostic implications as well as management differences. When evaluating coma we want to ensure the absence of things like eyelid apraxia (eyelid opening impairment), sedation that interferes with the exam, or brain death if it is present.

Localization of Coma

Structural causes of coma can occur due to injury to bilateral cerebral hemispheres, diencephalon (thalamus), or ascending reticcular activating system (midbrain and pons). In addition, there are numerous metabolic, infectious, and hormonal causes of coma (Table 58.1).

TABLE 58.1 Causes of Coma

Drugs/toxins
Opiates, alcohol, sedatives, amphetamines, barbiturates, tranquilizers, bromides, salicylates, acetaminophen, lithium, anticholinergics, lead, methanol, ethylene glycol, carbon monoxide, arsenic

Metabolic
Anoxia or hypoxia, hypercapnia, hypotension, hypoglycemia, hyperglycemia, diabetic ketoacidosis, hypernatremia, hyponatremia, hypercalcemia, hypocalcemia, hypermagnesemia, hypothermia, hyperthermia, Wernicke encephalopathy, hepatic failure, uremia, adrenal insufficiency, myxedema

Infectious/inflammatory

Bacterial, viral, or fungal meningitis/meningoencephalitis, acute disseminated encephalomyelitis, sepsis, malaria, Waterhouse-Friderichsen syndrome

Structural brain lesions

Subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic strokes, global cerebral hypoperfusion, cerebral venous sinus thrombosis, traumatic brain injury, hydrocephalus, basilar occlusion, central pontine myelinolysis, large hemispheric masses, pituitary apoplexy, cerebral abscess, or multifocal infection

Other

Nonconvulsive status epilepticus, catatonia, hypertensive encephalopathy, heat stroke, psychogenic coma

APPROACH TO COMA

Examination of the patient in coma is crucial for diagnosis and prognosis. Coma examination should begin with observation of the patient in their undisturbed state while taking note of any interactions with the environment. Initial examination should always focus on level of consciousness. If the patient is not awake at baseline, begin assessment of level of consciousness initially with verbal cues and subsequently with tactile stimulus. If there is no response to verbal cues and tactile stimuli, then assess response to noxious stimuli (sternal rub, supraorbital pressure, nail bed pressure). If the patient does not respond during the examination and the eyes remain closed, the patient is in a coma.

Further examination should focus on brainstem reflexes and motor responses. Examination of the brainstem reflexes cues the examiner to focal injury at the level of the midbrain, pons, or medulla. Examination should consist of testing the pupillary light reflex (assesses cranial nerves [CN] II and III), oculocephalic reflex (CN III, VI, and VIII), corneal reflex (CN V and VII), and cough and gag reflex (CN IX and X). Motor response should be aimed at assessing voluntary versus involuntary motor activity. In the patient in coma, motor examination can be assessed with noxious stimulus. Fold the arms on the patient's lap and administer a noxious stimulus. Differing responses include localization, withdrawal, flexor posturing, and extensor posturing. Care should be taken to note laterality. These

findings will allow calculation of the Glasgow Coma Scale (GCS) or Full Outline of UnResponsiveness (FOUR) score (Tables 58.2 and 58.3). When possible, the examiner may also assess tone, muscle bulk, and reflexes in the patient in coma to aid with localization.

TABLE 58.2 Glasgow Coma Scale

Best eye opening	
Spontaneous	4
With voice only	3
With pain only	2
None at all	1
Best verbal response	
Coherent speech	5
Confused intelligible speech	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal output	1
Best motor response	
Follows commands	6
Localizes pain stimuli[a]	5
Withdraws to pain stimuli	4
Decorticate posturing	3
Decerebrate posturing	2

No movements at all	1

[a]Localizing pain stimuli refer to gaze deviation, head turning, or hand movements toward the stimulus.

TABLE 58.3 Full Outline of UnResponsiveness Score

Eye response	
Eyelid open or opened, tracking, or blinking to command	4
Eyelids open but not tracking	3
Eyelids closed but open to loud voice	2
Eyelids closed but open to pain	1
Eyelids remain closed with pain	0
Motor response	
Thumbs-up, fist, or peace sign	4
Localizing to pain	3
Flexion response to pain	2
Extension response to pain	1
No response to pain or generalized myoclonus status	0
Brainstem reflexes	
Pupil and corneal reflexes present	4
One pupil wide and fixed	3
Pupil or corneal reflexes are absent	2
Pupils and corneal reflexes absent	1
Absent pupil, corneal, and cough reflex	0

Respiration	
Not intubated, regular breathing pattern	4
Not intubated, Cheyne-Stokes breathing pattern	3
Not intubated, irregular breathing	2
Breathes above ventilator rate	1
Breathes at ventilator rate or apnea	0

Vegetative state is defined as a state of wakefulness without awareness. These patients may have their eyes open and may even regard, but do not follow commands. Minimally conscious state represents a state where patients may be aware of the environment or themselves but with significantly impaired interaction with their environment. In a minimally conscious state, patients can have their eyes open, can regard, and can follow simple commands, but without much additional interaction. Coma, vegetative state, and minimally conscious state exist on a continuum of impaired consciousness.

DIAGNOSTIC STUDIES IN COMA

Initial screening of the patient in coma should be geared toward examination and diagnostics. During assessment in the emergency room, workup should include labs (glucose, sodium, calcium), drug screen, and imaging. Noncontrast head computed tomography (CT) should be the first line for imaging of all newly found patients in coma. Advanced imaging such as magnetic resonance imaging (MRI) or angiography can be completed after the patient is stabilized if it is deemed necessary. If laboratory data and imaging are negative, electroencephalography can be considered to evaluate for nonconvulsive seizures or lumbar puncture to evaluate for infectious or inflammatory causes of coma.

STABILIZATION OF THE PATIENT IN COMA

Stabilization of the patient in coma should occur in tandem with diagnostics. While care should be taken to maintain airway, breathing, and circulation (ABCs), GCS alone may not fully predict the need for intubation, and attention to whether the patient is able to manage secretions is paramount. For example, the patient with GCS score less than 8 may not necessarily require endotracheal intubation but the patient with GCS score 8 or more might. Airway protection refers to the maintenance of a patent passage of air from the mouth and nose to the lungs. Many patients with coma are able to maintain gas exchange (ie, normal oxygenation and ventilation) while spontaneously breathing. However, other factors should be considered when deciding whether to intubate the patient in coma, such as bulbar function, cough, and secretions. Some efforts to improve bronchial hygiene may help prevent or delay intubation, such as elevation of the head of the bed, strategic suctioning, and cough assist, and can be trialed in the carefully selected patient in coma to induce cough, clear secretions, and prevent atelectasis. However, for patients in coma that are not able to manage secretions, or fail efforts to improve bronchial hygiene, intubation is appropriate. When intubating the patient in coma, pharmacologic assistance including sedation and analgesia is indicated. Do not assume that the patient cannot sense pain because they are not awake. Use analgesia and sedation, in particular, when paralyzing this group of patients.

In addition to basic lifesaving treatments, the patient in coma often requires other management strategies. If history is unobtainable, C-spine precautions should be taken. In particular, with signs of other traumatic injuries such as bruising or fractures, C-spine protection with a C-collar should be performed. A nasogastric tube may be necessary both for aspirating gastric contents in the patient in coma and for alimentation. Exclude and treat hypoglycemia and opiate overdose. Physicians or nurses should perform neurologic examinations frequently. Hourly neurologic checks may be indicated in the acute setting.

Prognosis

Prognosis of the patient in coma depends upon the etiology of coma. Infectious, toxic, and metabolic causes of coma can be reversible and may carry a favorable prognosis. Conversely, coma from hypoxia depends on the associated neurologic findings. Some helpful tools to aid with prognostication in comatose survivors of cardiac arrest include pupillary light reflex, corneal reflex, motor response, somatosensory evoked potentials, neuron-specific enolase, and myoclonic status epilepticus on electroencephalogram (EEG).

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59 Declaration of Brain Death

Muhammad Waleed Zeb, Tina Kiguradze, and Peter Kang

History

Up until the mid-20th century, the clinical definition of death was widely regarded as the cessation of cardiopulmonary function. With advances in resuscitation, mechanical ventilation, and organ support, concerns arose regarding the presence of brain function in a patient whose life was supported by medical technology. In the late 1950s, with a growing number of patient cases with "particularly severe coma" or "beyond coma," physicians sought to define death by neurologic criteria. The concept of death of the neurologic system began to gain traction; however, many hesitated to equate it to cardiopulmonary death as they knew it. In 1968, a landmark report "A Definition of Irreversible Coma" was designed to address ethical issues surrounding the care of the "hopelessly unconscious patient." The subtitle of the report was "Definition of Brain Death." It stipulated four criteria that needed to be met for a patient to be considered in irreversible coma: "unreceptivity and unresponsivity," "no movements or breathing," absence of all brainstem reflexes, and isoelectric electroencephalography (EEG). Over the next decade, this new definition of brain death began gaining legal recognition. Its wide adoption, however, was prevented by a lack of consensus. In 1981, The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research released a report that aimed to unify the definition of brain death. It emphasized that the brain functioned as the principal integrator of bodily functions. Thus, death ensued when the "body's physiological system ceases to constitute an integrated whole." As a result, the **Uniform Determination of Death Act** was formulated in 1981, according to which death could be determined by (1) the "irreversible cessation of

circulatory and respiratory functions" or (2) the "irreversible cessation of all functions of the entire brain, including the brainstem." In 1995, the American Academy of Neurology published practice parameters in an attempt to standardize the neurologic criteria for brain death. The three fundamental criteria were "coma or unresponsiveness, absence of brainstem reflexes, and apnea," with a specific protocol provided for apnea testing. In cases where some components of the examination could not be reliably performed or evaluated, a set of "confirmatory tests" was proposed. Since then, with revisions to this protocol, there has been general acceptance of the notion of brain death among clinicians, major religions, and governments. However, there is variability in the practice of determining death by neurologic criteria. In the United States, these practices are generally determined at the institutional level with the exception of Nevada (The Nevada Statute), where statewide guidelines exist. The Nevada Statute is based on the American Academy of Neurology guidelines for declaration of brain death in adults and Pediatric Section of Society of Critical Care Medicine in infants and children.

Definition

Brain death is defined as the irreversible loss of all functions of the entire brain, including the brainstem, manifested by (1) complete loss of consciousness (coma), (2) absence of brainstem reflexes, and (3) absence of ventilatory drive (apnea). This determination must occur in the absence of any factors that indicate possible reversibility. Exception is made for neuroendocrine function (persistent function of antidiuretic hormone [ADH] and the lack of central diabetes insipidus) that may persist in patients with irreversible injury to the brain and brainstem, possibly due to the vascular anatomy of the hypothalamus and the pituitary that are supplied by extracranial vasculature.

Prerequisites

Brain death is a clinical diagnosis and given the medicolegal implications of this diagnosis, caution is warranted, and clinicians should ensure that certain criteria are met before performing the clinical examination. These include (1) a clinical history and etiology that is compatible with irreversible devastating brain injury that can lead to a complete loss of brain function, including the cerebrum and brainstem; (2) neuroimaging that is consistent with the clinical history and that demonstrates brain injury. This includes demonstration of severe intracranial hypertension and brainstem herniation (Figure 59.1A). Clinicians should reconsider testing if neuroimaging shows severe brain injury but is inconsistent with brain death (Figure 59.1B); (3) patient should have core temperature of more than 36 °C. This can be achieved with warming blankets, warmed fluids, or automated temperature regulation device if needed; (4) systolic blood pressure greater than 100 and mean arterial pressure greater than 60 with use of vasopressors and inotropes as needed; (5) allow for five elimination half-lives to pass if sedative medications have been administered. If hepatic or renal function is significantly impaired, it would be reasonable to wait for additional time to pass; (6) for patients who have received pharmacologic paralysis, train-of-four stimulator assessment should be done. If not available, deep tendon reflexes should be assessed; (7) toxicology screen should be obtained if there is concern for toxin exposure; (8) if alcohol intoxication is suspected, alcohol levels should be obtained; and (9) severe metabolic, endocrine, and acid-base derangements that could affect clinical examination should be corrected. If these findings cannot be corrected and are thought to be contributing to loss of brain function, ancillary testing should be pursued if the clinical presentation, examination, and apnea testing are all consistent with brain death.

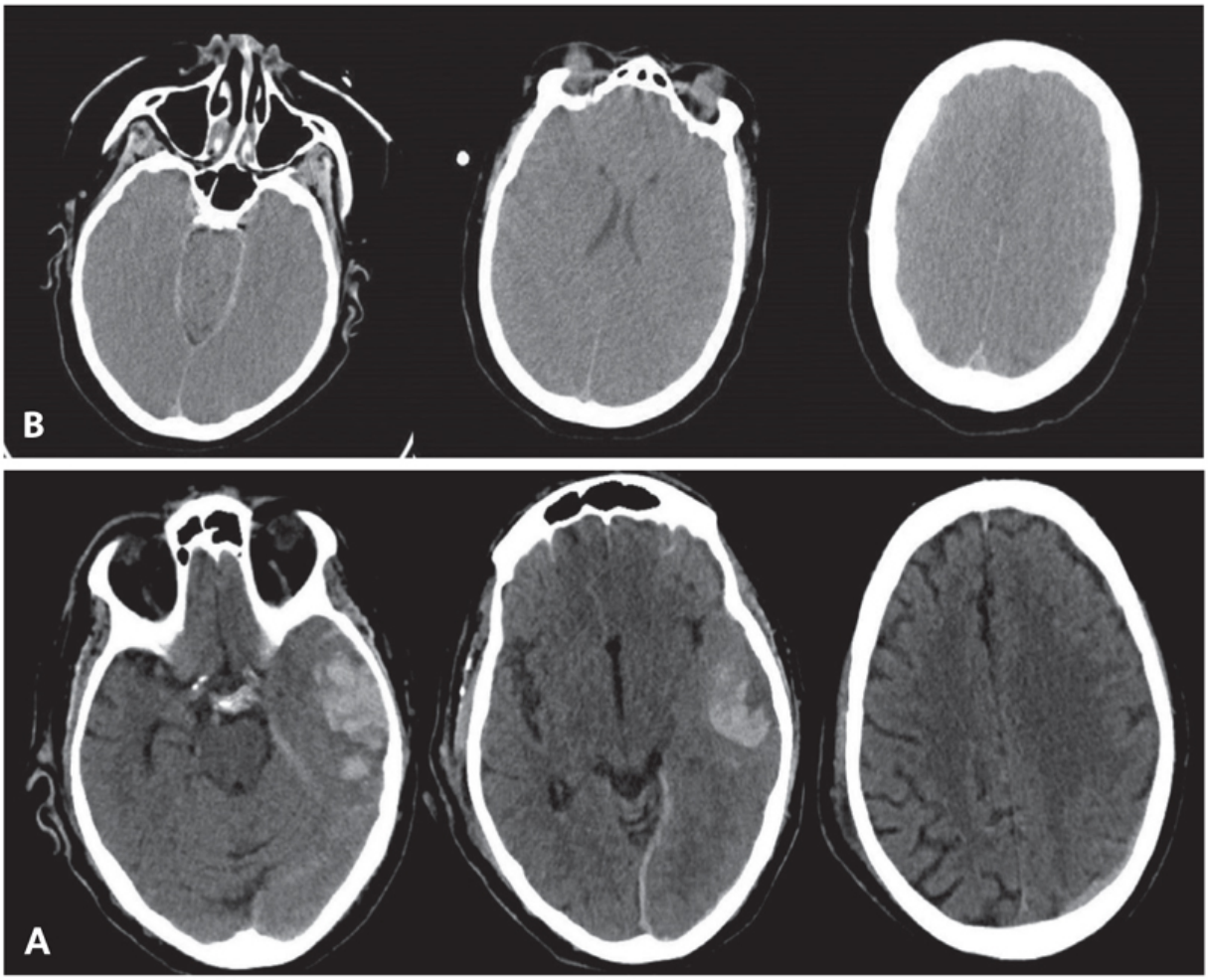

FIGURE 59.1 **A:** Computed tomography (CT) head with loss of gray-white differentiation, effacement of sulci, and obliteration of cisterns consistent with irreversible brain injury. **B:** CT head with intracranial, subdural, and subarachnoid hemorrhage but intact gray-white differentiation and normal sulci inconsistent with brain death.

Physical Examination

Once the clinician has ensured that all the prerequisites have been satisfied, they can proceed with the clinical examination. They should ensure to document vital signs, including the blood pressure and temperature, at the start of the physical examination. Examination begins with verification of unresponsive comatose state

to maximal external stimulation, including noxious stimulation. Central painful stimulus, which includes pressure at the supraorbital ridge and/or temporomandibular joint, should elicit no response, including grimacing, eye opening, or reflexive movements in extremities. Brainstem function should be assessed next. Midbrain function is assessed by checking for the pupillary reflex (cranial nerves II and III). Pupils should be mid-position or dilated, and there should be no pupillary constriction in response to bright light in either eye. Pinpoint pupils are not typical and should raise concern to the examiner. Pontine function is assessed by checking for corneal, oculocephalic, and oculovestibular reflexes. For the corneal reflex (cranial nerves V and VII), touch the cornea in each eye with a cotton swab along the external border of iris (corneal limbus). No eyelid movement should be seen. The oculocephalic reflex (cranial nerves III, VI, and VIII) is assessed by rotating the head horizontally in both directions. There should be no eye movement relative to the head movement. The intact response in a normal person is slow conjugate movement opposite the direction of head turning with or without a quick corrective saccade. Before checking for oculovestibular reflex (cranial nerves III, VI, and VIII), the auditory canal should be assessed for any obstruction that would prevent ice water from entering the canal and to ensure that the tympanic membrane is intact. The head of the bed should be elevated to 30° before irrigating with 30 mL of ice water for 60 seconds using a syringe attached to a catheter placed inside the canal. This should be repeated in the other ear after allowing 5 minutes to pass between checking each side. No eye movement should be observed in response to the irrigation of cold water. Medullary function is assessed by checking for cough and gag reflex. The gag reflex (cranial nerves IX and X) can be assessed by stimulating the posterior pharyngeal wall bilaterally with a tongue depressor or suction catheter; ideally, no response should be seen. The cough reflex (cranial nerve X, phrenic nerve, and spinal motor nerves) is assessed by passing the endotracheal tube suction catheter to the level of the carina with no cough response. Careful attention must be made to ensure the suction catheter is pushed down sufficiently,

which in most ventilator setups would require the catheter to be fully inserted. If all aforementioned brainstem reflexes are absent, the clinician should then apply deep pressure at the sternal notch followed by deep pressure in all four extremities to assess for any motor response other than spinally mediated reflexes. Examples of spinally mediated reflexes include triple flexion in the lower extremities, undulating toe, stereotyped flexion or extension of limbs, and the Lazarus reflex (lifting of flexed arms at the elbow followed by touching or crossing over each other on the chest). It should be noted that decorticate and decerebrate posturing are not compatible with brain death.

It is very important to understand that each part of the examination should be performed, and if one particular portion of the examination cannot be performed because of any circumstance, for example, orbital trauma that might preclude corneal, oculocephalic, oculovestibular, or pupillary reflex testing, ancillary testing should be pursued while still performing the remainder of the clinical examination and apnea test, if possible. The only exception is absence of a limb, in which case pain stimulus on that side of the body should suffice and no ancillary testing is required.

Apnea Test

The purpose of apnea test is to demonstrate the lack of drive for spontaneous respiration from the medullary respiratory centers despite adequate stimulus of hypercarbia and acidemia. Before initiating the test, the clinician should ensure that the patient is not generating any spontaneous respirations in the normocarbic state when put on spontaneous breathing mode on the ventilator for 1 minute. The flow trigger during this phase should be adjusted to 5 L/min to avoid false triggering due to water in the circuit, a bounding heart, or other ways that the ventilator might inadvertently deliver an assisted breath. After this, the patient should be pre-oxygenated with F_{IO_2} of 100% for at least 10 minutes. A baseline arterial blood gas

should be obtained. The patient's chest should be exposed to allow for observation of respiratory efforts. The patient should be disconnected from the ventilator and a catheter should be passed down the endotracheal tube with oxygen at a flow rate of 6 L/min. Care should be taken to avoid occluding the endotracheal tube, which prevents air from escaping. This could cause air trapping in the lungs, resulting in possible barotrauma or pneumothorax. If possible, the patient should be observed for approximately 10 minutes for any visible respiratory efforts. Before reconnecting the ventilator, a repeat arterial blood gas should be obtained. Special care should be taken to not perceive chest wall movement due to the beating heart as a sign of respiratory effort. The apnea test is considered positive if the $PaCO_2$ at the end of the testing is greater than 60 mm Hg and/or if there is a rise of 20 mm Hg above baseline. If the apnea testing cannot be completed for a full 8 to 10 minutes, for example due to desaturation or hypotension, an arterial blood gas should be obtained prior to or immediately after reconnecting to the ventilator. If the patient did not demonstrate respiratory effort despite significant hypercarbia, as seen on the blood gas, the apnea test is compatible with brain death. Patients who are apneic during the 10-minute test but do not reach the mentioned $PaCO_2$ goals should undergo repeat testing for a longer duration after reestablishing preoxygenation and normocarbia.

An arterial line, if not already present, should be established for close blood pressure monitoring and arterial blood gas sampling. The physician should also be prepared to up-titrate vasopressors during testing due to hypotension that can develop secondary to the hypercarbia and acidemia.

For patients who are hemodynamically unstable, requiring multiple vasopressors, or those with severe hypoxemic respiratory failure, it is reasonable to forego apnea testing and proceed directly to ancillary testing to avoid hemodynamic instability and possible cardiac arrest while performing apnea testing.

Ancillary Tests

Ancillary tests serve as surrogate means for completing brain death evaluation when components of the test cannot be safely or adequately performed (eg, concern for hemodynamic collapse during apnea testing or inability to perform oculocephalic or oculovestibular reflexes due to trauma).

The following are the ancillary tests to assess cessation of cerebral blood flow:

1. Four-vessel angiography: Four-vessel angiography is considered the gold standard test to evaluate cerebral blood flow. Brain death is confirmed in the absence of filling at the sites where the internal carotid and vertebral arteries enter the skull base, with a patent flow in the external carotid artery. Test limitations include the need to transport the patient to the angiography suite, significant use of resources, and the risks of an invasive procedure.
2. Radionuclide studies: This imaging uses ^{99m}TC-hexamethylpropylene amine oxime radiotracer. SPECT (single-photon emission computed tomography) is recommended over planar imaging. If SPECT is unavailable, perfusion scintigraphy with anterior and lateral planar imaging can be pursued. Brain death is confirmed in the absence of a tracer in the cerebral circulation but filling in the external cranial vasculature (empty lightbulb sign, Figure 59.2). False positive results can be observed if the imaging is performed in one plane instead of two planes (anterior and lateral). Typically, images are obtained at two time points that is, half-hour and 2 hours; but this may depend on institutional policies.
3. Transcranial ultrasound: Transcranial ultrasound measures pulsations of the middle cerebral arteries, vertebral arteries, the basilar artery, anterior cerebral arteries, and ophthalmic arteries. Brain death is confirmed if the ultrasound shows small peaked systolic pulsations or the absence of diastolic pulsations. It is

recommended that two examinations be performed at least 30 minutes apart. It is advised that the examinations be performed bilaterally, anteriorly, and posteriorly to include both internal carotid arteries as well as the vertebral and basilar arteries. Test limitations include reliance on the examiner's expertise and poor windows due to thick temporal bones (10% of patients have no acoustic windows). Transcranial Doppler should not be used in pediatrics in the absence of validation studies.

4. Computed tomography (CT) brain angiography and magnetic resonance (MR) brain angiography: At this time, it is recommended to avoid CTA and MRA for brain death evaluation given the lack of data regarding sensitivity and specificity of these modalities.

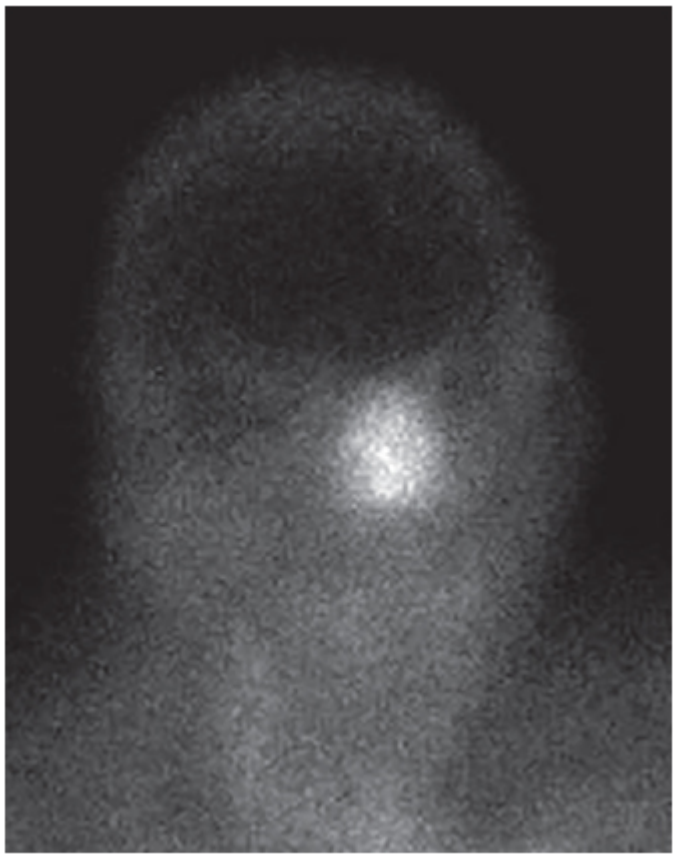

FIGURE 59.2 Empty lightbulb sign indicating absence of cerebral perfusion on perfusion scintigraphy imaging.

The following are the ancillary tests to assess loss of bioelectrical activity of the brain:

1. EEG: EEG sensitivity is set at 2 mcV and performed over 30 minutes. EEG may suggest brain death if there is no detectable electrical activity. Limitations include electromagnetic noise erroneously suggesting cerebral electrical activity, interobserver variability, and inability to assess brainstem function.
2. Somatosensory evoked potentials (SSEPs): SSEPs are elicited in response to bilateral median nerve stimulation. Absence of waveforms at the cortex may suggest brain death. Limitations include decreased specificity as SSEPs can be negative in isolated spinal cord and brainstem injuries.
3. Auditory and visual evoked potentials: Bilateral absence of waveforms through the brainstem to auditory and visual cortex may suggest brain death. Limitations include decreased specificity as they can be absent in isolated cranial nerve injuries and isolated brainstem lesions.

If ancillary tests assessing bioelectrical activity of the brain are used, they should be used in combination due to the abovementioned limitations.

Special Situations

EXTRACORPOREAL MEMBRANE OXYGENATION

The same principles apply for declaration of brain death in patients on extracorporeal membrane oxygenation (ECMO), including etiology, prerequisites, physical examination, apnea test targets, and ancillary testing. It is recommended that testing be performed in close collaboration with a cardiothoracic surgeon or intensivist. Apnea testing can be performed with both veno-arterial and veno-venous ECMO. The patient should be disconnected from the ventilator, and a catheter with oxygen flowing at a rate of 6 L/min

should be passed through the endotracheal tube. The sweep should be adjusted to 0.5 to 1 L/min to allow for retention of carbon dioxide while maintaining oxygenation through the membrane lung at 100%. With ECMO, it should be expected that the patient might not achieve a $Paco_2$ greater than 60 mm Hg or an increase greater than 20 mm Hg above baseline after 10 minutes without spontaneous respirations and may need longer periods of observation. For patients on veno-arterial ECMO with intrinsic cardiac output, blood gases should be obtained from both the arterial line and the post-oxygenator ECMO circuit at the same time with targets of $Paco_2$ greater than 60 mm Hg or increase greater than 20 mm Hg above baseline in both samples.

HYPOTHERMIA IN CARDIAC ARREST PATIENTS

Hypothermia may result in blunting of the brainstem reflexes and decreases the clearance of sedative medications that makes brain death evaluation challenging in patients undergoing targeted temperature management. Patients should be assessed at 24 hours after rewarming to more than 36 °C, and if the physical examination is consistent with brain death, neuroimaging should be obtained to assess for cerebral edema and brainstem herniation. In patients who received sedative medications, examination should be delayed until after five elimination half-lives of the drug administered, with the longest half-life have passed and would supersede the 24-hour waiting period after rewarming. Within the appropriate clinical context, if neuroimaging is consistent with severe intracranial hypertension secondary to cytotoxic cerebral edema and the physical examination is consistent with brain death, the patient may be declared brain dead. It would be reasonable to complete a second examination in 24 hours if there is uncertainty in the diagnosis. The authors recommend an attentive and careful approach with declaration of brain death in the setting of previous hypothermia.

Communication With Family

Involvement of family is an integral part of brain death evaluation given the complexity of the diagnosis and lack of education regarding brain death in the general population. Before initiation of brain death testing, the performing physician should approach the family and explain to them in simple terms what brain death means from the medicolegal perspective while keeping in mind the cultural and religious aspects that may be relevant. They should explain why their loved one is being evaluated for brain death and explain the rationale behind it. After this, the entire physical examination and apnea testing should be explained. At this point, a suggestion should be made that if apnea testing cannot be completed or specific aspects of the physical examination cannot be performed, ancillary testing might be needed. Family should be encouraged to stay in the room when performing the test, unless there is concern for interference with testing. Once the physical examination and apnea test have been completed and the patient is declared brain dead, the family should be updated regarding the findings, and any questions should be answered in detail.

Summary

(1) Brain death is a clinical diagnosis incorporating appropriate clinical context, physical examination, apnea test, and imaging. (2) Brain death is equivalent to cardiac death. (3) Specific criteria need to be met before a clinician begins brain death evaluation. (4) When certain components of physical examination and/or the apnea test cannot be performed, clinicians should be familiar with and perform ancillary tests to confirm brain death.

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60 Sedation and Delirium in the Intensive Care Unit

Lauren Sutton and Theresa Human

Sedation

Significant advances have been made in our understanding of how to provide physical and psychological comfort for patients in the intensive care unit (ICU). Important concepts to consider include ensuring reliable assessment tools are being used to evaluate pain, agitation, and delirium and establishing goals for each. Of the available sedation assessment scales, the Riker Sedation-Agitation Scale (SAS) (Table 60.1) and Richmond Agitation-Sedation Scale (RASS) (Table 60.2) are the most valid and reliable. Preventative strategies and protocol-driven dosing algorithms for pharmacologic interventions are key to keeping patients calm, comfortable, and cooperative in their care while minimizing doses of medications and avoiding oversedation.

TABLE 60.1 Riker Sedation-Agitation Scale (SAS)

7	Pulling at tube(s) or catheter(s), climbing over bed rails, striking at staff, thrashing
6	Requires restraints and frequent verbal cues, biting endotracheal tube
5	Anxious or physically agitated, calmed by verbal instructions
4	Calm, easily arousable, follows commands
3	Difficult to arouse but awakens to verbal stimuli or gentle touch; follows simple commands but drifts off again

2	Arouses to physical stimuli but does not communicate or follow commands, moves spontaneously
1	Minimal or no response to noxious stimuli, does not follow commands

TABLE 60.2 Richmond Agitation-Sedation Scale (RASS)

+4	Combative, violent, danger to staff
+3	Pulls or removes tube(s) or catheter(s); aggressive
+2	Frequent nonpurposeful movement, fights ventilator
+1	Anxious, apprehensive but not aggressive
0	Alert and calm
−1	Awakens to voice (eye opening/contact) ≥10 s
−2	Light sedation, briefly awakens to voice (eye opening/contact) <10 s
−3	Moderate sedation, movement or eye opening, no eye contact
−4	Deep sedation, no response to voice, but movement or eye opening to physical stimulation
−5	Unarousable, no response to voice or physical stimulation

Maintaining patient comfort, frequent reorientation, and optimization of the environment to maintain normal sleep-wake patterns are key interventions to reduce anxiety and agitation. Prompt identification and treatment of possible underlying causes of agitation, such as pain, hypoxemia, hypoglycemia, hypotension, fever, and alcohol or drug withdrawal, are important. Evidence from multiple randomized, controlled trials supports the use of the lowest possible level of sedation and dose of sedative for most ICU patients. Studies that compare level of sedation demonstrate that deeper sedation is associated with longer duration of mechanical

ventilation, increased tracheostomy rates, longer length of ICU stay, and reduced survival. Similarly, scheduled daily sedative interruptions and nurse-protocolized sedation have also shown to contribute to achieving lighter levels of sedation and using lower doses of benzodiazepine sedatives. These results need to be interpreted within the populations studied and may not apply to all ICU patients; for example, patients with intracranial hypertension, severe respiratory failure, concurrent treatment with neuromuscular blockers, and severe burns require deeper levels of sedation.

Despite the plethora of trials comparing sedative regimens, no sedative drug is clearly superior. Common agents used in the ICU include propofol, dexmedetomidine, and benzodiazepines (Table 60.3). Since the goal should be to minimize the depth and duration of sedation, short-acting agents without an active metabolite would be preferred. Additional considerations include indication, desired level of sedation, and acquisition cost. In studies that compared propofol to benzodiazepines, propofol did not reduce overall mortality. However, it did show a reduction in the ICU length of stay, shorter time to extubation, and shorter time to light sedation. Dexmedetomidine may also have advantages over benzodiazepines, as it does not cause respiratory depression and has some analgesic properties. When compared to benzodiazepines, dexmedetomidine resulted in less delirium and reduced mechanical ventilator days. However, it did not reduce hospital or ICU length of stay. When propofol and dexmedetomidine were compared, no difference in time at target sedation level, duration of mechanical ventilation, or ICU length of stay were noted. A meta-analysis comparing clinical outcomes in patients sedated with a benzodiazepine regimen to those sedated with nonbenzodiazepine regimens suggested a slightly longer length of stay and longer mechanical ventilation times in patients receiving a benzodiazepine-based regimen. In general, a nonbenzodiazepine-based regimen is recommended; however, the choice of sedative agent used should be driven by specific indications and sedation goals; the clinical pharmacology of the medication, including onset and offset; medication side effect profile;

and the patient's specific pathophysiology, including organ function and concomitant illnesses.

TABLE 60.3 Sedation Medications in ICU

Drug	Dose	Time to Arousal	Clinical Pearls
Midazolam (Versed)	Bolus: 1-5 mg IVP Infusion: 1-10 mg/h	Bolus: 1-2 h	• Reversed with flumazenil • Active metabolite may accumulate in renal dysfunction • Arousal time prolonged with continuous infusion due to active metabolite • Can be given IV/IM/nasal/infusion • Hepatic metabolism; cytochrome P450 substrate • Intubation required for infusion
Lorazepam (Ativan)	Bolus: 1-4 mg IVP	Bolus: 2-6 h	• Reversed with flumazenil • Can be given IV/PO/PT • Continuous infusion not recommended as propylene glycol toxicity may occur with high doses (symptoms include hypotension, bradycardia, lactic acidosis, hyperosmolality, and seizures).

Drug	Dose	Time to Arousal	Clinical Pearls
Propofol (Diprivan)	Infusion: 10-100 mcg/kg/min	10-15 min	• Caution propofol-related infusion syndrome (PRIS) *Characteristics of PRIS* • Metabolic acidosis • Cardiac dysfunction • Hyperlipidemia • Hyperkalemia • Rhabdomyolysis • Hypertriglyceridemia • Renal failure *Risk factors for development of PRIS* • Increased doses (>80 mcg/kg/min) • Prolonged infusion (>48 h) • Low BMI • Younger age • Concurrent vasopressor use • Dose-limiting ADR: hypotension • In a 10% lipid emulsion and provides 1.1 kcal/mL • May cause hypertriglyceridemia
Dexmedetomidine (Precedex)	Infusion: 0.1-1.5 mg/kg/h	6-10 min	• Does not cause respiratory depression • Does not achieve deep levels of sedation • Avoid bolus due to hypotension • Dose-limiting ADR: hypotension, bradycardia

Drug	Dose	Time to Arousal	Clinical Pearls
Ketamine	Bolus: 2 mg/kg IVP Infusion: 0.5-3 mg/kg/h	5-10 min	• Does not inhibit pharyngeal or laryngeal protective reflexes; no respiratory depression • May be beneficial in setting of bronchospasm or status asthmaticus • May cause hypertension, tachycardia, hypersalivation • Patients may experience reemergence hallucinations, which may be treated with low-dose benzodiazepines

ADR, adverse drug reaction; BMI, body mass index; ICU, intensive care unit; IM, intramuscular; IV, intravenous; IVP, intravenous push; PO, by mouth; PT, per tube.

Delirium

Delirium is recognized as a frequent and serious event that may occur in patients who are critically ill. Cognition is the most metabolically demanding process in the human organism and is easily disturbed by systemic or neurologic pathology, medications, or the routine of ICU care. Estimates for the incidence of delirium in the ICU range from 16% to 89%, although the diagnosis is often overlooked unless active bedside screening is implemented. Delirium remains a clinical diagnosis, with no diagnostic imaging or laboratory tests available to detect delirium. Delirium is associated with increased hospital length of stay, increased cost of care, and a risk of permanent cognitive disability.

Delirium is defined as an *acute* change in global cognitive function affecting attention, arousal, orientation, or perception. The course is usually fluctuating and symptoms often worsen at night. Knowing a patient's baseline cognitive ability is essential, as delirium must be

distinguished from dementia (a chronic problem of impaired cognition) and neurologic emergencies (cerebral herniation) producing an acutely decreased level of alertness. Risk factors with strong evidence for association with delirium can be found in Table 60.4. There are three types of delirium: hypoactive, hyperactive, and mixed. Patients with hyperactive delirium may be loud, agitated, and/or combative, eliciting a high degree of attention from staff. They often require medical and physical restraints. Hypoactive delirium is more common, particularly among the elderly; however, it tends to be overlooked and underdiagnosed. These patients may be quiet or sleepy yet profoundly confused and disoriented. Mixed delirium occurs when patients fluctuate between hyperactive and hypoactive delirium and is the most common type of delirium. Regardless of the type of delirium, the etiology is often the same. Patients with hypoactive delirium are least likely to survive, but those who do survive may have better long-term function than those with agitated or mixed delirium.

TABLE 60.4 Risk Factors for Delirium in the ICU

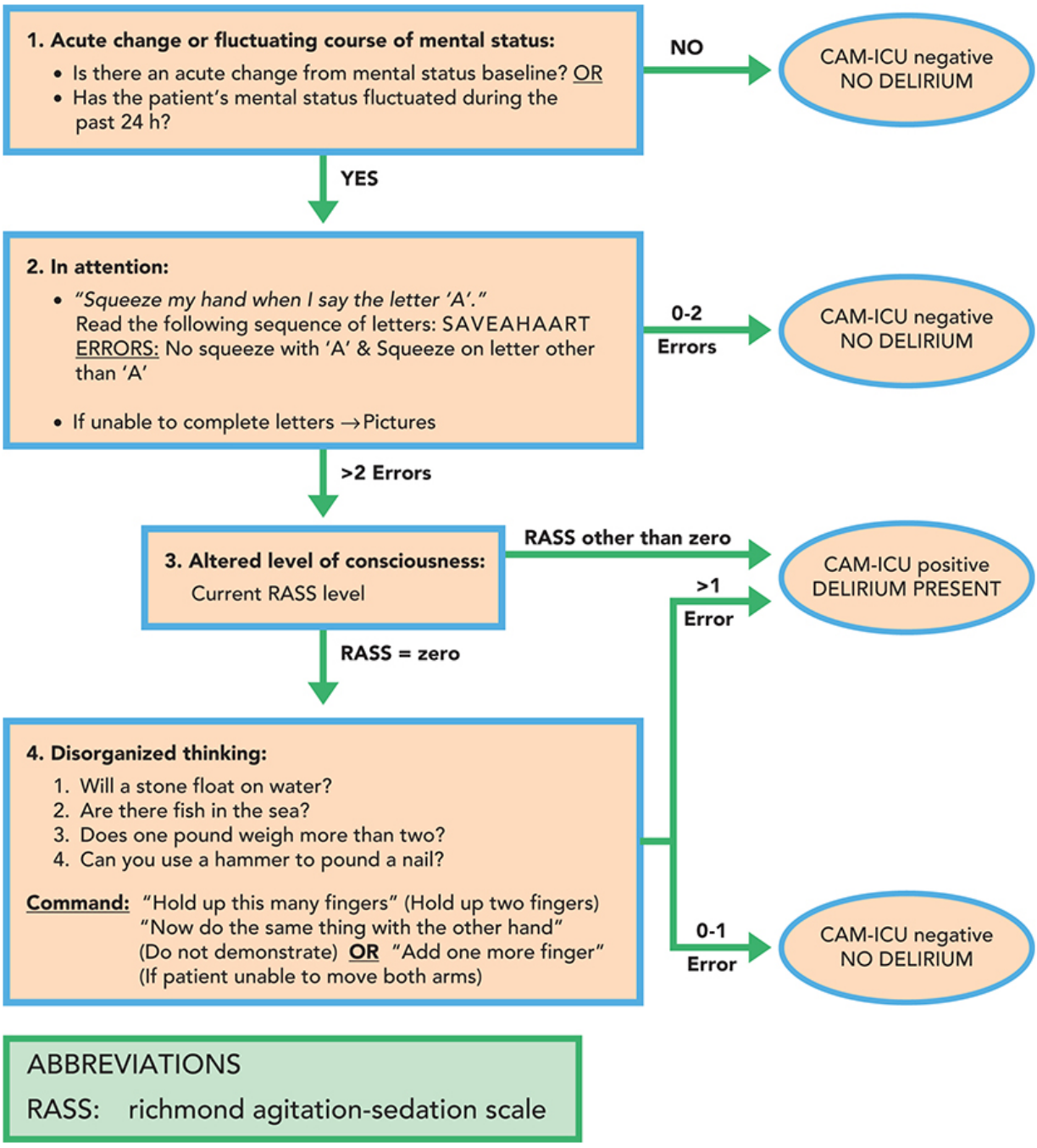
Modifiable	Nonmodifiable
Benzodiazepine use Blood transfusions	Greater age (data are variable) Preexisting dementia or cognitive impairment Prior coma Pre-ICU emergency surgery or trauma High severity of illness on admission Sedative-induced and multifactorial coma

ICU, intensive care unit.

All ICU patients should have routine bedside screening for delirium. The confusion assessment method for the ICU (CAM-ICU) (Algorithm 60.1) and the intensive care delirium screening checklist (ICDSC) (Figure 60.1) are the most valid and reliable delirium monitoring tools within the ICU. Both tools demonstrate reliable psychometric properties and are designed to detect delirium in both

intubated and nonintubated patients. Furthermore, both scales demonstrate high interrater reliability among practicing ICU nurses and physicians. The CAM-ICU reports an assessment at a single time point, whereas the ICDSC reports observations in symptoms over a period of time. Neither scale quantifies the severity of the delirium but rather report if it is present or not. Additionally, neither scale distinguishes hyperactive from hypoactive delirium; therefore, it is recommended to use in conjunction with an endorsed sedation assessment. Because delirium is a fluctuating change in the patient's mental status, patients should be screened more than 1 time per day (usually once per shift).

ALGORITHM 60.1 **Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet**


1. Acute change or fluctuating course of mental status:
• Is there an acute change from mental status baseline? OR
• Has the patient's mental status fluctuated during the past 24 h?
NO
CAM-ICU negative
NO DELIRIUM
YES
2. In attention:
• "Squeeze my hand when I say the letter 'A'."
Read the following sequence of letters: SAVEAHAART
ERRORS: No squeeze with 'A' & Squeeze on letter other than 'A'
• If unable to complete letters → Pictures
0-2
Errors
CAM-ICU negative
NO DELIRIUM
>2 Errors
3. Altered level of consciousness:
Current RASS level
RASS other than zero
CAM-ICU positive
DELIRIUM PRESENT
RASS = zero
4. Disorganized thinking:
1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weigh more than two?
4. Can you use a hammer to pound a nail?
Command: "Hold up this many fingers" (Hold up two fingers)
"Now do the same thing with the other hand"
(Do not demonstrate) OR "Add one more finger"
(If patient unable to move both arms)
>1
Error
0-1
Error
CAM-ICU negative
NO DELIRIUM
ABBREVIATIONS
RASS: richmond agitation-sedation scale

- Score your patient over the entire shift. Components do not all need to be present at the same time.
- Components #1-#4 require a focused bedside patient assessment. This cannot be completed when the patient is deeply sedated or comatose (ie, SAS = 1 or 2; RASS = –4 or –5).
- Components #5-#8 are based on observations throughout the entire shift. Information from the prior 24 h (ie, from prior 1-2 nursing shifts) should be obtained for components #7 and #8.

1. Altered level of consciousness Deep sedation/coma over entire shift [SAS = 1, 2; RASS = –4, –5] Agitation [SAS = 5, 6, or 7; RASS = 1–4] at any point Normal wakefulness [SAS = 4; RASS = 0] over the entire shift Light sedation [SAS = 3; RASS = –1, –2, –3]	= Not assessable = 1 point = 0 points = 1 point (if no recent sedatives) = 0 points (if recent sedatives)	No	0	1 Yes
2. Inattention Difficulty following instructions or conversation; easily distracted by external stimuli Will not reliably squeeze hands to spoken letter "A": SAVEAHAART		No	0	1 Yes
3. Disorientation In addition to name, place, and date, does the patient recognize ICU caregivers? Does patient know what kind of place they are in? (List examples such as dentist's office, home, work, hospital.)		No	0	1 Yes
4. Hallucination, delusion, or psychosis Ask the patient if they are having hallucinations or delusions (eg, trying to catch an object that is not there). Are they afraid of the people or things around them?		No	0	1 Yes
5. Psychomotor agitation or retardation EITHER: Hyperactivity requiring the use of sedative drugs or restraints to control potentially dangerous behavior (eg, pulling IV lines out or hitting staff). OR: Hypoactive or clinically noticeable psychomotor slowing or retardation.		No	0	1 Yes
6. Inappropriate speech or mood Patient displays inappropriate emotion, disorganized or incoherent speech, sexual or inappropriate interactions, or is apathetic or overly demanding.		No	0	1 Yes
7. Sleep-wake cycle disturbance EITHER: Frequent awakening/<4 h sleep at night. OR: Sleeping during much of the day.		No	0	1 Yes
8. Symptom fluctuation Fluctuation of any of the above symptoms over a 24-h period.		No	0	1 Yes
TOTAL SHIFT SCORE (Min 0 – Max 8)				

FIGURE 60.1 Intensive care delirium screening checklist (ICDSC). ICU, intensive care unit; IV, intravenous; RASS, Richmond Agitation-

Sedation Scale; SAS, Riker Sedation-Agitation Scale.

The workup of altered mental status in the ICU begins with knowledge of a patient's baseline cognitive function, including known dementia and level of functional independence. The timeline of the delirium is essential to distinguish the cause from a primary neurologic insult to the sequelae of medications, abnormal sleep patterns, and metabolic disturbances. It is important to see delirium as both an indication of an evolving pathology and a problem in itself that needs to be treated; giving a sedative without consideration of etiology may lead to masking a new issue.

The list of diagnoses that contribute to delirium is broad (Table 60.5). A careful neurologic examination, medication review, and basic laboratory studies will address most causes. Medications are among the most common causes of delirium in the ICU. In addition to newly added medications, recently discontinued medicines with a withdrawal potential, new drug interactions, or a change in the metabolism of previously tolerated medications should be considered. It is important to note the development of new-onset liver and/or renal dysfunction, as these may alter medication levels and their effect; elderly patients may become delirious even with "therapeutic" levels.

TABLE 60.5 Etiologies That Cause Delirium

Vascular	Stroke, hemorrhage, reversible posterior leukoencephalopathy, vasospasm, migraine
Toxins	Alcohol, illicit drugs, occupational exposures, carbon monoxide poisoning
Seizures	Aura, ictal state, nonconvulsive status epilepticus, postictal state
Other organs	Hepatic encephalopathy, uremia, cardiac disease, lung disease (hypoxemia, hypercarbia), thrombotic thrombocytopenic purpura

Electrolytes/metabolic	Hypo/hyperglycemia, hypo/hypernatremia, hypo/hypercalcemia, hypo/hypermagnesemia
Neoplastic	Primary tumor, metastases, carcinomatous meningitis, paraneoplastic syndromes, hyperviscosity
Infection	Urinary tract infection, pneumonia, meningitis/encephalitis, sepsis
Trauma	Direct trauma, edema, diffuse axonal injury, postconcussive syndrome, heat stroke, hypothermia
Autoimmune	Neuropsychiatric lupus, Hashimoto encephalopathy, CNS vasculitis, limbic encephalitis
Endocrine	Hypo/hyperthyroidism, hypopituitary state, hyper/hypoparathyroidism
Nutritional	Vitamin B_{12} deficiency, Wernicke encephalopathy (thiamine deficiency), Marchiafava-Bignami disease
Medication withdrawal	Appetite suppressants, cough/cold remedies, alcohol (even without delirium tremens), selective serotonin reuptake inhibitors, nicotine, baclofen, gabapentin, pregabalin, benzodiazepine
Medications	Anticholinergic agents, sedatives, antipsychotics, antiemetics, antispasmodics, tricyclic antidepressants, muscle relaxants, digoxin, anticonvulsants, corticosteroids, lithium, benzodiazepine, opioids, barbiturate

CNS, central nervous system.

If the cause of delirium is not found, neurologic consultation should be considered. Serious conditions can exhibit subtle findings or even a nonfocal examination. For instance, strokes in the nondominant hemisphere can cause delirium in the absence of hemiparesis, or fluent aphasia may be mistaken for delirium. Patients experiencing nonconvulsive status epilepticus may have no symptoms except delirium. Lumbar puncture, electroencephalography, brain imaging,

and more specific laboratory studies are usually warranted in these cases.

PREVENTION OF DELIRIUM

Studies suggest that early mobilization in ICU patients may reduce the incidence and duration of delirium, shorten ICU and hospital length of stay, and lower hospital cost. There are a small number of trials suggesting that prophylactic pharmacologic agents may reduce delirium incidence in specific subsets of patients; however, no difference in other clinical meaningful outcomes was identified. Therefore, prophylactic agents are generally not recommended.

TREATMENT OF DELIRIUM

A methodical and thorough approach will help identify the cause of delirium in most cases and should guide treatment. Nonpharmacologic strategies should be utilized to reduce delirium. Some useful techniques that may combat the contribution of routine ICU care to the development of delirium include having family members bring familiar objects (glasses, hearing aids, clocks, calendars, photographs of friends and family) to the bedside and regular reorientation of the patient by a familiar person. Placing patients in rooms with natural light helps restore normal sleep-wake cycles, and, if possible, efforts should be made to limit stimulation at night. Sedation should also be minimized to improve wakefulness and early mobilization strategies should be employed. Next, one should consider pharmacologic etiologies, such as drug interactions and withdrawal syndromes, and efforts made to eliminate potential inciting medications (Tables 60.5 and 60.6). Neurologic and neurosurgical causes should also be sought and treated appropriately. Finally, one should address and correct any metabolic derangement or dysfunction.

TABLE 60.6 Environmental Contributors That Cause Delirium

Cause	Treatment
Disorientation	Frequent reorientation
Sleep cycle change	Provide stimulating activity, keep out of bed during day, minimize interruptions at night
Sensory deficits	Put on glasses, hearing aids, dentures
Poor communication	Communication devices
Catheters, restraints	Remove catheters, tubes, and restraints as early as possible
Dehydration	Assess for dehydration and hydrate
Malnutrition	Feed with enteral nutrition (or parenteral, if needed)
Pain	Assess for and treat pain
Immobility	Remove restraints early, range-of-motion exercises, promote early mobility
Urinary retention	Place a bladder catheter or start scheduled catheterizations
Constipation	Disimpact if needed, start bowel regimen/routine
Fever	Antipyretics, scheduled if necessary
Infection	Identify and treat underlying infection
Hypoxemia, hypercarbia	Check arterial blood gases, ventilate, or oxygenate as needed

If delirium persists despite treating possible causes or if treating the underlying etiologies is not feasible, one can consider treating symptoms pharmacologically. While initial data showed that atypical antipsychotics may reduce the duration of delirium in adult ICU patients, several subsequent studies have conflicting results.

Patients treated with antipsychotics need to be carefully monitored for fever or rigidity (indicating neuroleptic malignant syndrome), extrapyramidal symptoms (tremors, stereotypic movements, dystonia), and QT interval prolongation, which can lead to fatal arrhythmias. All patients should have a baseline electrocardiogram. Due to the lack of benefit seen in trials, coupled with significant adverse effects, and potential morbidity and financial cost if agents are continued outside of the ICU, pharmacologic agents should be reserved for patients with significant distress secondary to delirium or for those who are agitated and may be a danger to themselves or staff members. Although hypoactive delirium is more common, we do not recommend trying to improve level of consciousness in the acute setting with activating medications.

Dexmedetomidine may be utilized in mechanically ventilated patients where agitation is inhibiting ventilator weaning or extubation and should be considered the drug of choice in patients with delirium that require continuous intravenous sedative infusions. Two randomized controlled trials comparing dexmedetomidine to benzodiazepines for sedation showed an approximate 20% reduction in delirium in the dexmedetomidine group. It is not clear whether dexmedetomidine reduced the incidence of delirium or if benzodiazepines increased the risk for delirium in this population. Additional data have shown that dexmedetomidine in patients with hyperactive delirium receiving mechanical ventilation results in more ventilator-free hours and quicker time to resolution of delirium than standard of care. Currently, no additional data exist to recommend other sedation agents to treat delirium.

Conclusion

Our ability to effectively diagnosis, treat, and manage pain, agitation, and delirium in the ICU is key to reduce cost and improve ICU outcomes. A multidisciplinary, protocolized approach can significantly assist clinicians in identifying the diagnosis, direct choice of treatment goals, and assist in mitigating oversedation with

sedation algorithms. Central to these principles is that pain should always be addressed simultaneously.

SUGGESTED READINGS

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61 Acute Spinal Cord Disorders

Terrance T. Kummer

Acute spinal cord injury (SCI), a form of myelopathy, may be traumatic or nontraumatic (Table 61.1). Traumatic SCI affects approximately 18,000 individuals annually in the United States. Causes include motor vehicle collisions, falls, recreational accidents, and acts of violence. Nontraumatic causes of myelopathy include ischemia, hemorrhage, infection, autoimmune conditions, and neoplasms. SCI may cause devastating lifelong disability with major health, psychological, and financial impacts, especially if one considers that injuries most commonly occur in the second to fourth decade of life, when victims are in their most productive years. Despite extensive public educational campaigns, licensing requirements, and public safety measures, SCI continues to increase in prevalence.

TABLE 61.1 Causes of Spinal Cord Injury

- Traumatic and degenerative (compression fractures, disk herniation)
- Vascular (infarction, epidural hematoma, arteriovenous malformations)
- Infections (abscesses, myelitis, empyema, tuberculosis)
- Inflammatory/demyelinating (transverse myelitis, acute disseminating encephalomyelitis, multiple sclerosis)
- Neoplastic (tumors and metastases, post radiation)
- Other (vitamin B_{12} deficiency, syringomyelia, amyotrophic lateral sclerosis, spinal canal stenosis, spondylosis)—usually more chronic course

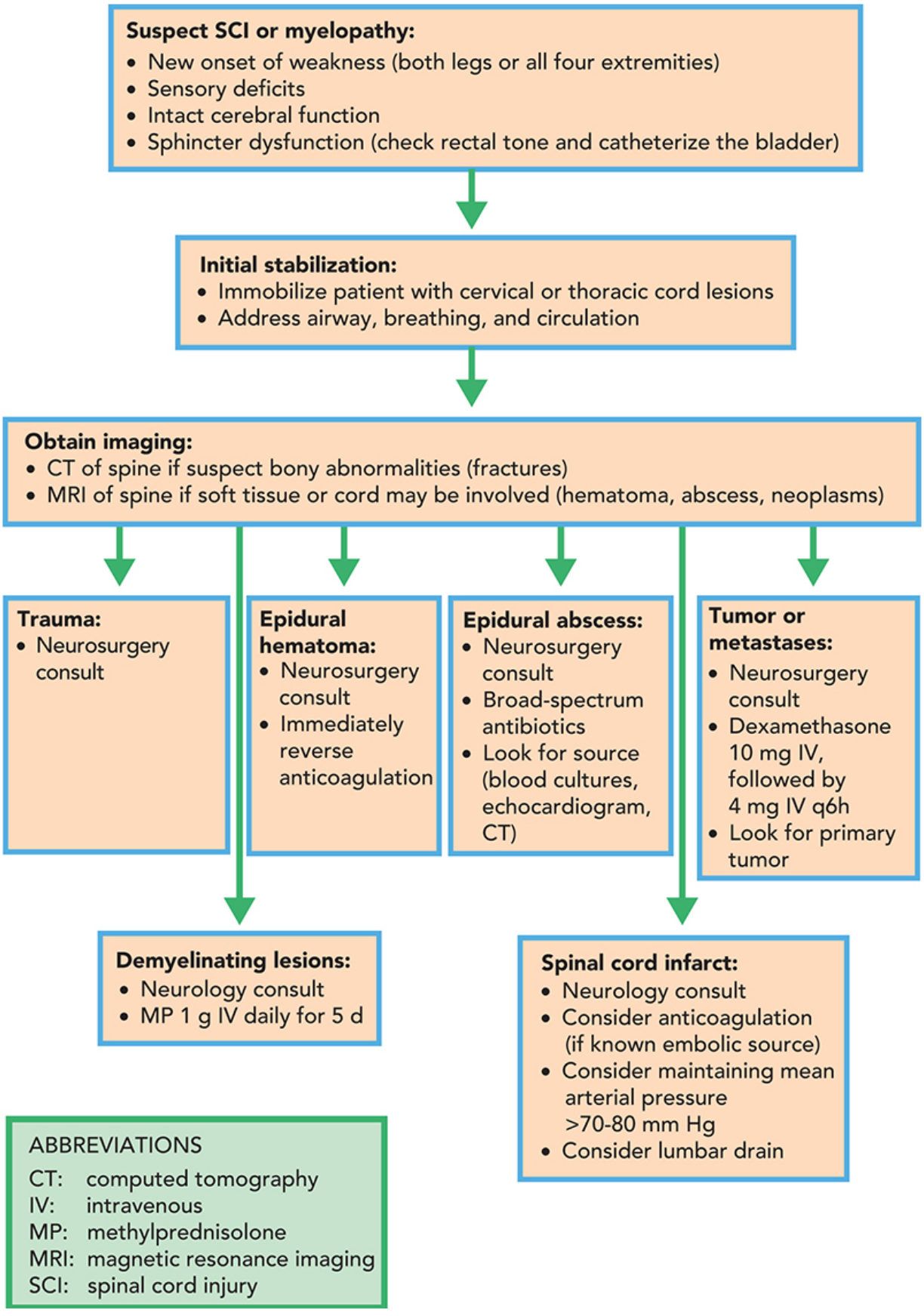
SCI should be approached as a medical emergency. Certain types of myelopathy can be reversed if addressed at the right time. Prompt recognition of clinical symptoms is imperative. The usual clinical

presentation involves a triad of motor impairment (classically symmetric but can be asymmetric), sensory loss, and sphincter dysfunction (ie, urinary retention or incontinence of stool and/or urine) with preservation of cerebral function (unless there is concomitant brain injury). Pain at the corresponding level of the spine is not always present. A group of well-described syndromes help localize the level of the injury (Table 61.2). Algorithm 61.1 presents a detailed initial approach to the patient with SCI. In addition to surgical care and medical interventions for improving neurologic outcome, intensive care unit (ICU) management may be necessary because of systemic complications of SCI.

TABLE 61.2 Spinal Cord Syndromes

- Complete transection—loss of bilateral motor and sensory function below level
- Hemisection (Brown-Sequard syndrome)—loss of ipsilateral motor and proprioception/vibration; contralateral loss of pain and temperature
- Central cord—impairment of hands and arms more than legs
- Ventral cord—loss of motor and all sensory modalities except proprioception/vibration
- Dorsal cord—preservation of motor (usually) and pain/temperature, loss of proprioception/vibration
- Cauda equina—extremely painful, asymmetric, lower motor neuron findings, late urinary retention
- Conus medullaris—less painful, symmetric, mixed upper and lower motor neuron findings, early urinary retention

ALGORITHM 61.1 Initial Approach to a Patient With Suspected SCI/Acute Myelopathy


Suspect SCI or myelopathy:
• New onset of weakness (both legs or all four extremities)
• Sensory deficits
• Intact cerebral function
• Sphincter dysfunction (check rectal tone and catheterize the bladder)
Initial stabilization:
• Immobilize patient with cervical or thoracic cord lesions
• Address airway, breathing, and circulation
Obtain imaging:
• CT of spine if suspect bony abnormalities (fractures)
• MRI of spine if soft tissue or cord may be involved (hematoma, abscess, neoplasms)
Trauma:
• Neurosurgery consult
Epidural hematoma:
• Neurosurgery consult
• Immediately reverse anticoagulation
Epidural abscess:
• Neurosurgery consult
• Broad-spectrum antibiotics
• Look for source (blood cultures, echocardiogram, CT)
Tumor or metastases:
• Neurosurgery consult
• Dexamethasone 10 mg IV, followed by 4 mg IV q6h
• Look for primary tumor
Demyelinating lesions:
• Neurology consult
• MP 1 g IV daily for 5 d
Spinal cord infarct:
• Neurology consult
• Consider anticoagulation (if known embolic source)
• Consider maintaining mean arterial pressure >70-80 mm Hg
• Consider lumbar drain
ABBREVIATIONS
CT: computed tomography
IV: intravenous
MP: methylprednisolone
MRI: magnetic resonance imaging
SCI: spinal cord injury

Traumatic Spinal Cord Injury

Cervical cord injury is the most common type of traumatic SCI. Traumatic brain injury occurs concomitantly in up to half of these patients; just as many may have injuries to other organs. Almost 50% of victims of cord trauma will present with “spinal shock,” a condition characterized by flaccid areflexic paralysis and lack of sensation in all modalities caudal to the location of the injury. Some patients may even experience symptoms rostral to the actual injury level. Spinal shock usually improves in the first few days post injury.

Spine stability is assessed with multiple-view plain films, computed tomography (CT), and often magnetic resonance imaging (MRI) (to evaluate for ligamentous injury) to direct surgical intervention or guide stabilization with collars or other external stabilizing devices. The appropriate type of spinal imaging is dictated by the mechanism of trauma and suspicion for spinal injury. Surgical decompression, when required, is usually emergent. The surgical plan and the stability of the spine are important factors for intensivists to consider, as limitations of mobility (“log roll precautions”) and neck extension are important for airway management. Immobilization, performed to limit secondary cord damage due to improper positioning of the unstable spine, is not without its own risks, such as worsening intracranial hypertension, airway compromise, diminished chest wall mobility, pressure sores, and pain.

NEUROPROTECTION

There are no proven neuroprotective agents for SCI. In the past, high-dose methylprednisolone infusion was common. A critical review of prior studies, however, does not support this tradition, and the practice has fallen out of fashion as multiple societies have stated there is insufficient evidence to recommend its use. There is, however, evidence that methylprednisolone results in increased mortality in moderate-to-severe traumatic brain injury, which often

coexists in traumatic SCI. A number of additional experimental therapies are under investigation, but none are proven effective or are in widespread use clinically.

CARDIOVASCULAR MANAGEMENT

Many patients with cervical or upper thoracic cord injury may develop neurogenic shock (note neurogenic shock is different from spinal shock, described earlier) because of the interruption of the spinal sympathetic chain. Decreased sympathetic innervation to the heart and blood vessels results in cardiovascular depression with bradycardia, hypotension, and low systemic vascular resistance. Hemodynamic monitoring is advisable and treatment with fluids and vasopressors to preserve organ perfusion is essential. Vasopressors with chronotropic/inotropic features (norepinephrine, dopamine) are preferred to augment cardiac function as well as to increase vascular tone. The optimal blood pressure goal is unclear; experimental data show that hypotension further worsens SCI due to hypoperfusion. Limited evidence suggests there may be a benefit to augmentation of blood pressure, though this remains unproven. As a result, the practice of maintaining mean arterial pressure at supraphysiologic levels (>85 mm Hg) for several days post injury is inconsistently implemented. Atropine should be kept at bedside for severe bradycardia. Transcutaneous pacing may be needed in rare refractory cases.

AIRWAY AND BREATHING

The most common indication for endotracheal intubation after SCI is for high cervical injuries that impair diaphragmatic function. Injuries above the level of C5 almost universally require at least transient mechanical ventilation. Injuries at C3 or above often result in respiratory arrest. Endotracheal intubation is recommended for those cord trauma victims who have associated traumatic brain injury with a Glasgow Coma Scale score less than 8 or signs of elevated intracranial pressure. Any airway compromise due to focal edema,

fractures, and/or hemorrhages of the neck may also require intubation. Only physicians with advanced airway skills should attempt intubation with an unstable spine. Fiberoptic intubation is often required as the cervical spine often cannot be manipulated. Measures should be taken to avoid hypotension during intubation. Succinylcholine is contraindicated in cases in which SCI occurred over 24 hours ago. Neurosurgeons should be at bedside to help with spine immobilization if the cervical collar or halo must be removed.

Close respiratory monitoring in a critical care setting is generally necessary as SCI victims encounter multiple pulmonary complications (neurogenic pulmonary edema, pneumonia, atelectasis, pleural effusions, pulmonary embolism) and are prone to respiratory failure even days after the initial injury. Patients who require extensive operative courses with or without prone positioning may have massive fluid shifts in the first few postoperative days and are at risk for rapid pulmonary edema. This is particularly dangerous in combination with limited neck mobility. Keep in mind that with lesions below C5, while diaphragmatic function is generally preserved, intercostal muscles may be compromised leading to diminished lung volumes, poor cough, aspiration, and hypoventilation.

THROMBOEMBOLISM PREVENTION

Patients with SCI are at high risk for the development of deep venous thromboses, especially in the first 3 months after injury. Prophylactic inferior vena cava (IVC) filter placement, however, is not indicated. Surveillance Doppler venous studies are an option. Pneumatic compression devices should be applied as soon as possible. Pharmacologic prophylaxis (low-molecular-weight heparin or unfractionated heparin) should be started as soon as possible after trauma or surgery, generally within 2 days of surgery, when the risk of bleeding is acceptable. Therapeutic anticoagulation should generally be withheld in the immediate postoperative period. Placement of an IVC filter may be required if a deep venous thrombosis develops.

GASTROINTESTINAL MANAGEMENT

Acute gastroparesis may require gastric suctioning and administration of prokinetic agents to avoid aspiration. Ileus and constipation commonly complicate the course in patients with SCI. A bowel regimen (eg, scheduled laxatives, suppositories every other day) should be instituted early to prevent fecal impaction. H_2 antagonists are indicated in these patients for prophylaxis of stress ulcer and gastrointestinal bleeding.

SKIN

Patients with SCI are highly prone to pressure ulcers. Frequent alteration of position to allow pressure relief and meticulous care of wounds is necessary. Low air-loss suspension beds and automatically rotating beds may diminish the incidence of pressure ulcers and facilitate healing of existing ulcers.

OTHER ISSUES

Spasticity and contractures become a major problem within weeks post injury. Early physical and occupational therapy should be initiated. Baclofen, diazepam, and dantrolene are potentially useful agents for spasticity. Pulmonary, urinary tract, and cutaneous infections are common. Universal precautions for ventilator-associated pneumonia should be instituted. Urinary retention is seen commonly and may require self-catheterization or indwelling catheters. Pain and depression are common and should be addressed promptly. A pain management specialist is often helpful, and psychological support systems are essential.

Nontraumatic Myelopathy

Most patients with nontraumatic SCI do not require ICU admission unless the upper cord is involved, in which case, it is important to identify those at risk for respiratory failure or hemodynamic instability

and supply the supportive care described earlier. Treatment for nontraumatic myelopathy is tailored to the condition and may involve surgical and/or medical interventions. Further discussion of nontraumatic myelopathy is outside the scope of this chapter.

SUGGESTED READINGS

American College of Surgeons; Trauma Quality Programs. Best practice guideline for spine injury. 2022. https://www.facs.org/media/k45gikqv/spine_injury_guidelines.pdf

Evidence-based best practice guidelines on the management of spine and spinal cord injury.

62 Neuromuscular Disorders in the Critically Ill

Joshua Newman, Charles Andrew Roach, and Robert C. Bucelli

Neuromuscular medicine is a field that encompasses a broad spectrum of disorders extending from the lower motor neurons in the brainstem and spinal cord to the nerve roots, peripheral nerves, neuromuscular junctions, and muscles. Disorders of these components of the nervous system may lead to neuromuscular respiratory failure (NMRF), dysphagia, focal or generalized weakness, and sensory loss. NMRF is a particular concern in patients who are critically ill and is often under-recognized in its early phases, as patients may not appear to be in respiratory distress due to weakness inhibiting the recruitment of accessory muscles or the ability to raise their respiratory rate, as observed in other forms of respiratory failure. Knowledge of early signs and appropriate monitoring for NMRF can aid in early recognition and treatment. NMRF can be related to the primary indication for admission, such as Guillain-Barré syndrome (GBS) or myasthenic crisis, but can also develop in patients who are critically ill without a history of neuromuscular disease (eg, myosin loss myopathy). This chapter will review NMRF monitoring, diagnosis, etiologic differential diagnosis, and management, as well as specific disorders that critical care providers should be familiar with, including motor neuron diseases, GBS, myasthenia gravis (MG), myosin loss myopathy, and rhabdomyolysis/malignant hypothermia.

Neuromuscular Respiratory Failure

The most common neuromuscular disorders that lead to NMRF are GBS, MG, amyotrophic lateral sclerosis (ALS), and critical illness myopathy (CIM). Weakness of the diaphragm and the intercostal muscles leads to hypoventilation and weak cough with poor clearance of secretions. Ultimately, patients can develop hypercarbic respiratory failure, but this occurs as a very late finding in NMRF. Relying on routine monitoring techniques, such as pulse oximetry and blood gases, will not detect NMRF until very late in the course when decompensation is imminent. Symptoms of dyspnea on exertion and orthopnea are common in the setting of diaphragm weakness. Assessment of neck flexion and extension strength is a reasonable indicator of diaphragm strength as many of these muscles share myotomes with the diaphragm. A hypophonic voice, dysarthria, dysphagia, and weak cough are also common in neuromuscular patients at risk of developing NMRF.

Objective bedside spirometry to measure negative inspiratory force (NIF) and forced vital capacity (FVC) are useful in the initial assessment and subsequent monitoring of patients with, or at risk of developing, NMRF. NIF is the maximal inspiratory pressure generated after forceful exhalation, as measured with a mouthpiece attached to a pressure gauge. Normal NIF values in most individuals can be less than −100 cm H_2O (ie, the lower the number the better), but values greater than −60 cm H_2O are always considered abnormal. Values rising above −30 (toward 0), in the absence of technical issues with good effort, suggest prominent neuromuscular respiratory dysfunction, particularly diaphragm dysfunction. Most patients require mechanical ventilation at values above −20 cm H_2O. FVC measures the amount of air exhaled, and values below 30 mg/kg or a drop greater than 20 mg/kg should alert the clinician to monitor more closely and may warrant initiating noninvasive and/or mechanical ventilation. Spirometry to monitor NIF and FVC can be performed serially by a respiratory therapist every 6 to 24 hours. More frequent spirometry may induce fatigue, which is an important consideration in patients with neuromuscular disorders, such as MG, where fatigue is often a major component of the pathology. Facial

weakness is common in patients with NMRF and may prevent them from forming a tight seal around the mouthpiece. A poor seal may result in artifactually abnormal measurements or exaggerate abnormal values. A facemask sealed tightly against the lips may overcome this issue of poor mouth seal. An additional consideration is the potential need for a nose clip, in that palatal weakness may result in leak through the nose when trying to exhale through the mouth. Trends in these parameters, reconciled with other standard clinical features of respiratory distress, should guide management more than an isolated abnormal value, particularly in patients with inconsistent or unreliable measurements.

Intubation in NMRF should be performed electively when signs of imminent NMRF are present, rather than pursuing this intervention emergently when patients tire out and/or develop hypercapnia or hypoxemia related to atelectasis or aspiration. Neuromuscular-blocking agents should be avoided. Depolarizing neuromuscular blockers like succinylcholine can provoke lethal hyperkalemia in patients with denervation, such as axonal GBS variants. Nondepolarizing neuromuscular blockers can cause prolonged paralysis in patients with MG, and these patients are at high risk of myosin loss myopathy (discussed in more detail later). A trial of noninvasive ventilation with bilevel positive airway pressure (BiPAP) can be attempted in patients with NMRF if their mental status, physical ability to remove the mask, and airway reflexes are preserved. This scenario can often be employed for patients with MG. However, if the patient is progressively worsening, such as a patient with GBS who has not reached their nadir, a trial of BiPAP is unlikely to avoid intubation, and intubation should be performed early/prophylactically (Tables 62.1 and 62.2).

TABLE 62.1 Etiologies of Neuromuscular Respiratory Failure by Localization

Localization	Timing of Insult	Differential Diagnosis

Localization	Timing of Insult	Differential Diagnosis
Brain/high cervical spinal cord	Prior to admission	Brainstem/spinal cord infarct or hemorrhage, acute brainstem or high C-spine inflammatory lesion
	ICU-acquired	Perioperative spinal cord ischemia, epidural hematoma, postoperative abscess, osmotic myelinolysis
Anterior horn cell	Prior to admission	Acute flaccid paralysis (West Nile virus, Enterovirus D68 or A71, polio), ALS with decompensation
Nerve/root	Prior to admission	GBS, vasculitic neuropathy, paraneoplastic, porphyria, heavy metal poisoning (arsenic), diphtheria
	ICU-acquired	Critical illness polyneuropathy (controversial), phrenic nerve injury
Neuromuscular junction	Prior to admission	Myasthenia gravis, organophosphate poisoning, LEMS (respiratory failure much less common than MG), botulism Pediatrics: botulism, myasthenia gravis, tick paralysis
	ICU-acquired	Prolonged NMJ blockade, hypermagnesemia
Muscle	Prior to admission	Immune myopathy, acid maltase deficiency (ie, Pompe disease), metabolic myopathies (lipid storage)
	ICU-acquired	Critical illness myopathy (specifically myosin loss myopathy), acute necrotizing myopathy, rhabdomyolysis

GBS, Guillain-Barré syndrome; LEMS, Lambert-Eaton myasthenic syndrome; MG, myasthenia gravis; NMJ, neuromuscular junction.

TABLE 62.2 Signs of Impending Neuromuscular Respiratory Failure

Sign	Red Flag
Clinical:	Quadriplegia
Progressive weakness	Inability to lift head off bed
Bulbar involvement	Dysphagia, weak voice
Weak cough	Bifacial weakness
	Trouble clearing secretions
	"Wet" voice
Respiratory Complaints:	Complains of respiratory fatigue
Orthopnea (early)	Unable to speak in full sentences
Dyspnea	Unable to count to 20 on single breath
Tachypnea	Nocturnal desaturations, prefers to sit up
Accessory muscle use	Using neck and abdominal muscles to breath
Abdominal paradox	Inward motion of abdomen with inspiration
Signs of Distress:	Restless
Tachycardia	Staccato speech
Diaphoresis	
Monitoring:	Vital capacity <15-20 mL/kg
Vital capacity	Drop in vital capacity by 30% from baseline
Arterial oxygen saturation	Desaturation (late sign)
Arterial $Paco_2$	Hypercapnia = hypoventilation (late sign)
Chest x-ray	Reduced lung volumes, atelectasis, pneumonia

Motor Neuron Diseases

Motor neuron disease (MND) refers to a group of disorders that lead to dysfunction of upper motor neurons that originate in the precentral gyrus, lower motor neurons of the brainstem and spinal cord, or both. As implied by the name, these disorders do not affect sensory fibers, so complaints of numbness, tingling, or neuropathic pain should be absent unless there are confounding variables. The most common MND in the adult population is ALS, which in its classic

form affects both upper and lower motor neurons. Symptoms evolve over months to years, and cardinal clinical features include asymmetric limb weakness, muscle wasting, limb stiffness, dysphagia, dysarthria, and NMRF. A mixture of upper and lower motor neuron signs are found on examination, including atrophy, fasciculations, hyper- and/or hyporeflexia, and spasticity of the limbs and/or speech. The diagnosis is based on clinical features and exclusion of alternative diagnoses. Electrodiagnostic testing can aid in the diagnostic evaluation.

Individuals with ALS may present to the intensive care unit (ICU) due to NMRF. Unfortunately, most available treatments (rare exceptions noted for individuals with certain hereditary forms of disease) are of limited benefit in slowing disease progression. Palliative care is a useful resource for symptom management (eg, muscle cramps and spasticity, sialorrhea, constipation, depression/anxiety) and when assisting with goals of care conversations.

Acute flaccid paralysis (AFP) is a disease of lower motor neurons within the spinal cord and brainstem, frequently associated with viral infections. Poliovirus was the predominant cause historically, but in recent years, this has now been eclipsed by West Nile virus (WNV) and enteroviruses (eg, EV-D68). Clinically, patients with West Nile neuroinvasive disease (WNND) may present with a range of neurologic signs that range from aseptic meningitis to severe encephalitis with myeloradiculopathy following a prodrome of fever, malaise, GI symptoms, and headache. The presence of encephalopathy may delay recognition of weakness due to a neuromuscular etiology.

Cerebrospinal fluid (CSF) analysis in WNND initially shows neutrophilic pleocytosis that shifts to lymphocytic predominance within a few days. Protein is elevated and glucose is normal. Spinal cord MRI may show increased T2/FLAIR signal or enhancement of the ventral horns and/or nerve roots. MRI of the brain can show abnormalities in the thalami and/or basal ganglia. Detection of the virus by polymerase chain reaction (PCR) is very difficult as the virus

is quickly cleared, but the diagnosis can be confirmed with elevated CSF WNV IgM antibody titers.

Treatment of AFP involves the recognition and management of respiratory failure and bulbar dysfunction. There are no proven benefits to antiviral or immunomodulatory therapies.

Guillain-Barré Syndrome

GBS is a term used to describe a group acute immune-mediated polyradiculoneuropathies that are distinguished from one another by clinical and electrophysiologic characteristics. The most common of these subtypes in the United States and Europe is acute inflammatory/immune demyelinating polyradiculoneuropathy (AIDP), in which patients typically present with acute ascending paralysis and paresthesias following an upper respiratory or diarrheal illness. The disease often progresses to quadriplegia with involvement of cranial nerves. Respiratory failure requiring mechanical ventilation occurs in approximately 20% of cases, and autonomic dysfunction is common. The course is monophasic, with maximal disability usually occurring within 2 weeks, and by definition within 4 weeks, of symptom onset. Treatment is with either intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), as there is no proven benefit to one intervention over the other. There is no evidence to suggest that combining these therapies (also known as “stacking”) provides any additional benefit, and it is important to avoid using PLEX after IVIg to prevent eliminating the therapeutic effect of the IVIg.

In a patient who is suspected of having GBS, a neurologic examination should be performed focusing on eye movements, facial and bulbar strength, limb strength, and reflexes. These are important to follow over time given the progressive, often rapidly progressive, nature of GBS. Atypical historical or examination features may prompt evaluation for mimics such as spinal cord lesions. These can be evaluated with MRI of the spinal cord, which should be obtained with and without contrast to help detect nerve root enhancement, a fairly common finding in GBS. A lumbar puncture should be obtained

to look for albuminocytologic dissociation (ie, elevated CSF protein without leukocytosis), though elevation in protein may not be seen early in course and should be repeated if the diagnosis remains in question. Leukocytosis (>10 white blood cells [WBC] for most in practice and undoubtedly when >50 WBC per guidelines) in the CSF should prompt evaluation for other conditions that may mimic GBS (eg, HIV, WNV, cytomegalovirus, sarcoidosis, neoplasms). Electromyography/nerve conduction studies (EMG/NCS) should be used in the initial evaluation, but this can be normal or show only subtle abnormalities early on. Serial studies may be required to help differentiate among different GBS subtypes. There is growing evidence of a potential diagnostic and prognostic role for serum neurofilament light chain in the early recognition of acute axon injury in these conditions.

Patients with GBS often require admission to the ICU for management of respiratory failure and autonomic dysfunction. The general principles of NMRF were covered earlier in the chapter. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) has been validated to predict respiratory failure within the first week of illness and is available for use through online medical calculator tools. Nearly half of patients who require ventilation will go on to need tracheostomy. Patients should be closely monitored for autonomic dysfunction, including ileus, constipation, urinary retention, labile blood pressures, and cardiac arrhythmias. Caution should be exercised in treating blood pressure due to potential lability, and atropine should be kept at bedside as suctioning may induce bradycardia.

As soon as the diagnosis is made, treatment should be initiated with either IVIg 2 g/kg over 2 to 5 days or with 5 to 6 total plasma volume exchanges over the course of 10 to 14 days. These treatments have supportive clinical trial data, and neither has been proven to be superior to the other. There is no role for corticosteroids in the treatment of GBS.

Many patients with GBS have near-complete recovery, but residual disability is more likely in those with diarrheal prodrome, older age, severe weakness, need for mechanical ventilation, and

evidence of axon loss on EMG/NCS. The modified Erasmus GBS Outcome Score (mEGOS) is an internationally validated clinical prediction model that can be applied early in the disease course to predict the probability of being unable to walk independently during the first 6 months after illness. This tool can now be accessed through several online medical calculators. **There is no evidence supporting retreatment** with either IVIg or PLEX in cases of less desirable outcomes.

Myasthenia Gravis

Autoimmune MG is an immune-mediated disease with antibodies directed against components of the neuromuscular junction resulting in impaired neuromuscular transmission. Approximately 85% of cases have antibodies directed against the acetylcholine receptor (specifically “binding” antibodies). The other 15% have serum antibodies targeting muscle-specific kinase (MuSK) or are seronegative. The impairment in neuromuscular synaptic transmission leads to fatigable weakness, a clinical hallmark of the illness. MG can be isolated to the ocular muscles (ptosis, ophthalmoparesis, and diplopia) or can be generalized and involve bulbar muscles (facial weakness, dysarthria, dysphagia), neck, and limb muscles (common for upper limbs to be worse than lower limbs with preferential weakness of forearm and finger extensors).

Myasthenic crisis is NMRF due to diaphragm and other respiratory muscle weakness in a patient with MG. Myasthenic crisis is a neurologic emergency often requiring ICU care and ventilatory support. Myasthenic crisis occurs in approximately 20% of patients over the course of their disease. It is often precipitated by a trigger like MG medication noncompliance or weaning, infection, surgery, or certain medications. Transient worsening of MG can be seen in a subset of patients if they are started acutely on a high dose of steroids (typically >20 mg/d).

MG is primarily a clinical diagnosis. Over 90% of patients with MG have oculobulbar weakness, and the presence of these symptoms

should trigger MG as a differential diagnosis. However, oculobulbar deficits are not requisite for the diagnosis. Diagnostic testing used to confirm a clinical diagnosis of MG includes the detection of antibodies targeting acetylcholine receptor (AChR) (specifically binding subtype) or MuSK and/or electrophysiologic evidence of abnormal neuromuscular transmission (detected by repetitive nerve stimulation [RNS] or single-fiber EMG). Chest imaging should be obtained to evaluate for an associated thymoma, as MG is paraneoplastic in a notable percentage of patients. However, thymectomy should be delayed until crisis is controlled to avoid postoperative worsening/disease exacerbation. Ice pack testing is not routinely used, but is easily performed at the bedside, and Tensilon testing is no longer recommended. Single-fiber EMG is more sensitive (but less specific) than RNS, but is often unavailable in the ICU setting when there is concern for myasthenic crisis or impending crisis.

MG treatment consists of symptomatic treatment, immunomodulatory treatment, and supportive care.

Symptomatic treatment is with acetylcholinesterase inhibitors like pyridostigmine (Mestinon). Pyridostigmine can be helpful to manage fluctuating symptoms in the outpatient or non-ICU inpatient setting, but in the ICU setting in a patient with NMRF, pyridostigmine is typically held as the increased secretions caused by the medication can contribute to aspiration and respiratory failure in patients with bulbar weakness. High doses of pyridostigmine can also cause increasing weakness in the setting of cholinergic toxicity, a syndrome accompanied by a combination of excessive tearing, salivation, diarrhea, sweating, cramps, and fasciculations.

Immunomodulatory treatments are commonly divided into acute therapies and chronic regimens, the latter more pertinent to the outpatient setting. Accordingly, we will focus here on acute treatments. For patients presenting in myasthenic crisis or in a myasthenic exacerbation with impending crisis (eg, profound bulbar dysfunction), the two primary therapeutic interventions are identical to GBS, that is, PLEX and IVIg. Efficacy is equal, and rates of adverse events are similar between PLEX and IVIg.

Access/institutional familiarity, comorbidities, and relative contraindications are often used in deciding between these two therapies. In the absence of relative contraindications, most experts recommend PLEX over IVIg, given its faster onset of action. As is the case with GBS, PLEX should be avoided after IVIg, and there is no evidence to support stacking therapies. There is no role for high-dose pulse corticosteroids in the management of MG exacerbation or myasthenic crisis. In fact, pulse corticosteroids are likely to do more harm in this setting (see later). Regardless of the therapy pursued, it is important to recognize that while the effects of these treatments are rapid, they are often short-lived. Prednisone for maintenance therapy is typically started (or increased from baseline dose) during the course of PLEX or IVIg. Starting prednisone at a goal maintenance dose (eg, ~0.8 mg/kg of ideal body weight) while a patient is actively in crisis carries a high risk of worsening the acute exacerbation and/or precipitating myosin loss myopathy. Accordingly, once a patient is stabilized with IVIg or PLEX, it is generally safe to start prednisone at a dose of 10 to 20 mg daily and increase by 5 mg every 3 to 7 days to a target dose of 50 to 60 mg daily. The prednisone takes months to have full effect and can be weaned, albeit much more slowly than is typical of most other immune-mediated disorders, in the outpatient setting. Recovery tends to be more rapid than in GBS cases. Most patients do not require prolonged intubation or tracheostomy.

Ventilatory support is typically required for patients presenting with MG crisis. MG patients presenting with myasthenic crisis can often be trialed on BiPAP as long as they are protecting their airway. Studies of ventilatory management in myasthenic crisis have shown that the majority of patients treated initially with BiPAP are able to avoid intubation, and a reliable predictor of failing BiPAP is a P_{CO_2} greater than 45 mm Hg at the time of BiPAP initiation. Use of BiPAP results in shorter ICU stays. If MuSK antibodies are identified, consideration should be given to initiating rituximab after PLEX or IVIg. Efgartigimod (Vyvgart) is a new type of MG treatment that may be considered for both acute and maintenance therapy. This

treatment is given in cycles of four weekly infusions of 10 mg/kg. Efgartigimod works by reducing IgG levels, including levels of the pathogenic antibodies.

As with other neurologic autoimmune diseases, it is necessary to evaluate for and treat any infectious or metabolic trigger that may be contributing to the exacerbation. The diagnosis of MG does not preclude use of any specific antibiotic if it is strongly indicated, but certain antibiotics do carry a theoretical risk of worsening MG control (refer to Table 62.3). Paralytic agents should be avoided in sick patients with MG, as they are at increased risk of myosin loss myopathy (a form of CIM), which can result in prolonged weakness and NMRF.

TABLE 62.3 Myasthenia Gravis Differential Diagnostic Considerations and Distinguishing Features

Myasthenia gravis	Fluctuating weakness of eyelids, extraocular muscles, nasal dysarthria, limb weakness that is worst in triceps and/or finger extensors	EDx shows decrement on repetitive nerve stimulation, standard EMG is usually normal.
ALS	Chronic course until inciting event like aspiration/pneumonia, notably spares the eyes until very late in the disease, hyperreflexia	EMG shows active and chronic denervation in multiple body regions.
Immune myopathies	Symmetric proximal greater than distal limb weakness more affected than oculobulbar function, different EDx features	EMG shows small, short duration myopathic motor units and often shows membrane irritability.
GBS or subacute CIDP	Absent reflexes, distal and proximal limb weakness, ascending progression, elevated CSF protein (particularly after day 7 post-onset)	EDx shows reduced MUP recruitment and loss of F waves early, acquired demyelinating neuropathy features appear later.

Botulism	Predominantly in children, descending weakness, autonomic symptoms	NCS shows small CMAP amplitudes with increment post-exercise or fast RNS. EMG often shows membrane irritability.

ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; EDx, electrodiagnostics; EMG, electromyography; GBS, Guillain-Barré syndrome; MUP, motor unit potential; NCS, nerve conduction studies; RNS, repetitive nerve stimulation.

Rhabdomyolysis, Malignant Hyperthermia, and Critical Illness Myopathy

Rhabdomyolysis is the acute breakdown of skeletal muscle tissue leading to release of muscle fiber contents, including muscle enzymes and myoglobin, into the blood. The classic triad of the syndrome of rhabdomyolysis is acute muscle pain, proximal weakness, and myoglobinuria that develop over hours to days. However, less than 10% of patients manifest with the full triad. Rhabdomyolysis has a wide variety of causes and can be broadly categorized into traumatic, nontraumatic exertional, or nontraumatic nonexertional. Table 62.4 summarizes common causes within each category. The diagnosis of rhabdomyolysis is often made in the emergency department or ICU in patients who are weak, complain of muscle pain, or have dark urine and are found to have a markedly elevated creatine kinase (CK). There is no strict consensus CK cutoff value for rhabdomyolysis, but most experts and sources report ranges of 10,000 to over 200,000 for acute rhabdomyolysis. Myoglobin rises earlier and normalizes earlier in the course of rhabdomyolysis than CK. When a patient's dark urine clears, this indicates normalization of myoglobin levels and cessation of active muscle breakdown. CK levels will lag behind myoglobin, peak at 3 to 5 days, and slowly decline over the following 6 to 10 days. **Accordingly, frequent serial CK measurements in the setting of**

rhabdomyolysis are not clinically helpful. The better parameter to monitor is urine myoglobin or looking for blood on urinalysis in the absence of red blood cells on microscopy (as the assay used for urinalysis has cross-reactivity between hemoglobin and myoglobin). The acute management of rhabdomyolysis involves monitoring for and managing electrolyte derangements and renal function, as well as identifying and removing any triggers. The most common electrolyte abnormalities resulting from rhabdomyolysis are hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and metabolic acidosis. Acute kidney injury develops in approximately 15% to 50% of cases and may require temporary renal replacement therapy. Cardiac dysrhythmias can arise in the setting of these electrolyte abnormalities, and patients should be closely monitored with telemetry. Immune myopathies can present with rhabdomyolysis, but often have a more subacute course. Immune myopathies are an important differential diagnostic category to consider, as treatment with steroids or other immunomodulatory treatments is necessary and indicated, as opposed to the supportive care described earlier for rhabdomyolysis (Algorithm 62.1).

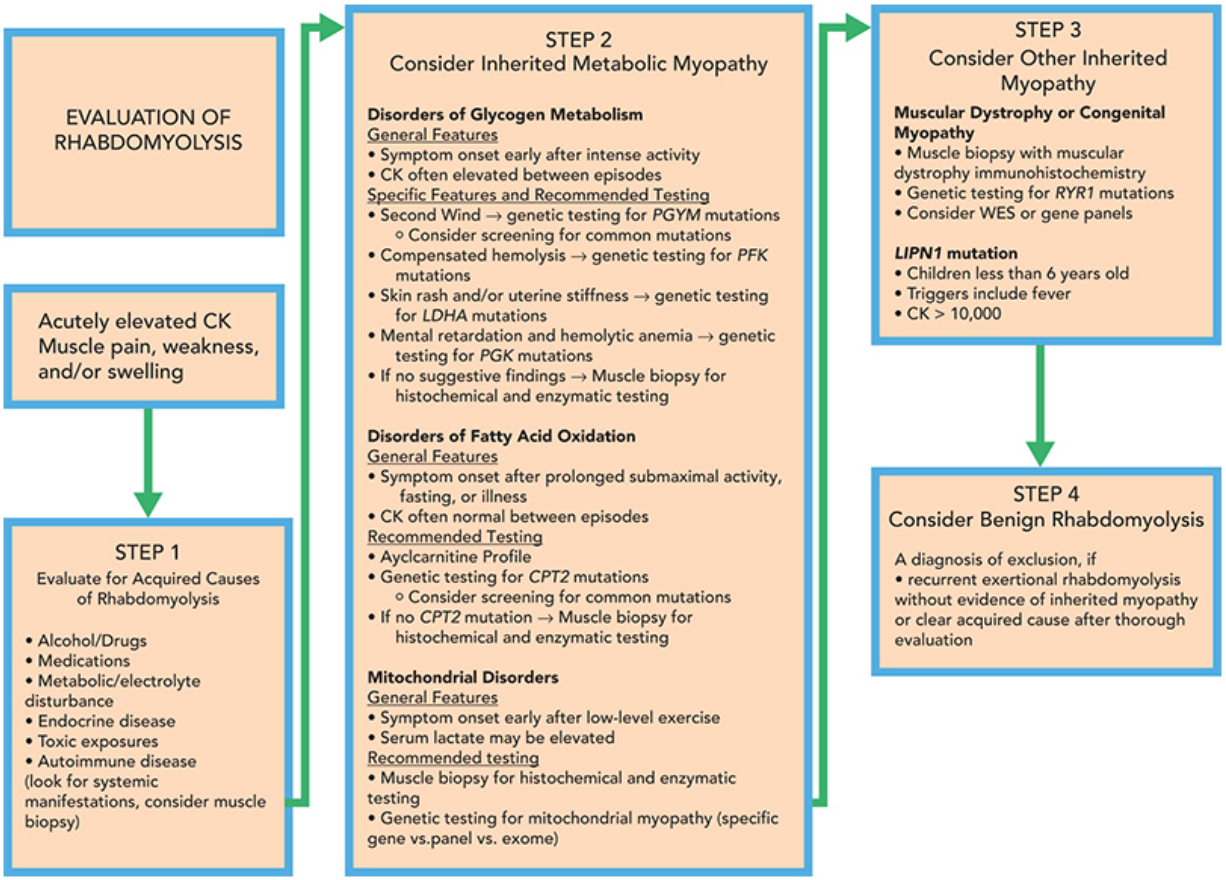
TABLE 62.4 Rhabdomyolysis Etiologies by Category

Category	Etiologies
Traumatic	Crush syndrome, compartment syndrome, prolonged immobilization, electrical or burn injury, compression of vascular supply to muscle
Nontraumatic, exertional	Marked exertion in untrained individual, eccentric exercises, hyperthermia, prolonged convulsive status epilepticus, metabolic or other myopathies
Nontraumatic, nonexertional	Drug exposure,[a] toxin exposure, infections (viral, sepsis), electrolyte disorders, immune and inflammatory myopathies

[a]Common drugs associated with rhabdomyolysis include statins, colchicine, amiodarone, and daptomycin. Antipsychotics, especially first generation, may

cause acute creatine kinase (CK) elevation in context of neuroleptic malignant syndrome. Prolonged exposure to propofol carries a risk of rhabdomyolysis.

ALGORITHM 62.1 **A Diagnostic Algorithm for Patients With Rhabdomyolysis**


EVALUATION OF RHABDOMYOLYSIS
Acutely elevated CK
Muscle pain, weakness, and/or swelling
STEP 1
Evaluate for Acquired Causes of Rhabdomyolysis
• Alcohol/Drugs
• Medications
• Metabolic/electrolyte disturbance
• Endocrine disease
• Toxic exposures
• Autoimmune disease
(look for systemic manifestations, consider muscle biopsy)
STEP 2
Consider Inherited Metabolic Myopathy
Disorders of Glycogen Metabolism
General Features
• Symptom onset early after intense activity
• CK often elevated between episodes
Specific Features and Recommended Testing
• Second Wind → genetic testing for PGYM mutations
◦ Consider screening for common mutations
• Compensated hemolysis → genetic testing for PFK mutations
• Skin rash and/or uterine stiffness → genetic testing for LDHA mutations
• Mental retardation and hemolytic anemia → genetic testing for PGK mutations
• If no suggestive findings → Muscle biopsy for histochemical and enzymatic testing
Disorders of Fatty Acid Oxidation
General Features
• Symptom onset after prolonged submaximal activity, fasting, or illness
• CK often normal between episodes
Recommended Testing
• Ayclcarnitine Profile
• Genetic testing for CPT2 mutations
◦ Consider screening for common mutations
• If no CPT2 mutation → Muscle biopsy for histochemical and enzymatic testing
Mitochondrial Disorders
General Features
• Symptom onset early after low-level exercise
• Serum lactate may be elevated
Recommended testing
• Muscle biopsy for histochemical and enzymatic testing
• Genetic testing for mitochondrial myopathy (specific gene vs.panel vs. exome)
STEP 3
Consider Other Inherited Myopathy
Muscular Dystrophy or Congenital Myopathy
• Muscle biopsy with muscular dystrophy immunohistochemistry
• Genetic testing for RYR1 mutations
• Consider WES or gene panels
LIPN1 mutation
• Children less than 6 years old
• Triggers include fever
• CK > 10,000
STEP 4
Consider Benign Rhabdomyolysis
A diagnosis of exclusion, if
• recurrent exertional rhabdomyolysis without evidence of inherited myopathy or clear acquired cause after thorough evaluation

(From Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. *Muscle Nerve*. 2015;51(6):793-810. Figure 1.)

Malignant hyperthermia (MH) is defined as a hypermetabolic crisis that occurs when a malignant hyperthermia susceptible (MHS) individual is exposed to inhaled volatile anesthetics or succinylcholine. Individuals with MHS derive their susceptibility from autosomal dominantly inherited gene mutations. The most commonly mutated gene is *RYR1*. Less commonly mutated genes associated with risk of MH include *SCN4A*, *CACNL2A*, a locus on chromosome 3q13.1, *CACNA1S*, and a chromosome 5p locus. MHS individuals

may have an idiosyncratic reaction to anesthetic agents, so a prior history of tolerating these drugs does not exclude the possibility of MH. The earlier signs of MH are a rapid rise in $ETCO_2$ that is resistant to adjustments in minute ventilation, tachycardia, and hyperthermia with rapidly rising temperature. Patients will become diffusely rigid and may have masseter spasm. Oxygen saturation will drop as a result of high CO_2. The pathophysiology is incompletely understood in many cases, but in individuals with MHS, these anesthetic agents result in persistently elevated cytoplasmic calcium levels in muscle cells resulting in sustained contraction with inability to relax the muscle fiber contractile apparatus. Sustained contraction leads to anaerobic metabolism, lactic acidosis, failure of the Na-K ATPase pump, and, ultimately, rhabdomyolysis of myocytes. As a result, patients can develop similar electrolyte imbalances and arrhythmias, as described in the prior section on rhabdomyolysis. The treatment is to immediately stop the offending anesthetic agent and immediately initiate dantrolene 1 mg/kg every 4 to 8 hours. Dantrolene works by inhibiting the RYR1 receptor on the myocyte sarcoplasmic reticulum to stop the cycle of calcium release into the myocyte cytoplasm.

CIM is the most common form of ICU-acquired neuromuscular weakness. CIM may develop in greater than 25% of patients who are intubated and mechanically ventilated in the ICU for at least 7 days. Risk factors include sepsis, multiorgan failure, and exposure to high-dose corticosteroids, and/or neuromuscular-blocking paralytics. Clinical manifestations include symmetric, flaccid generalized limb weakness that frequently involves the ventilatory muscles leading to failure to wean from the ventilator. Extraocular and facial muscles are often relatively spared. Tendon reflexes are often, but not always, reduced or absent. There may be a transient period early in the course when CK is elevated, but often by the time CIM has been clinically recognized, CK levels are normal or even low/undetectable (<20). EMG/NCS can show either irritable features (ie, fibrillations and positive sharp waves) or nonirritable myopathic changes, along with low-amplitude compound muscle action potentials with a

signature prolonged repolarization phase. Muscle biopsy shows selective loss of myosin filaments and, less commonly, necrotic fibers. Management is supportive. Recovery is often prolonged but can be complete with appropriate physical and occupational therapy, treatment of underlying infections, and avoidance of further exposure to steroids or neuromuscular-blocking agents, if possible.

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63 Traumatic Brain Injury and Elevated Intracranial Pressure

Terrance T. Kummer

Severe head trauma is a leading cause of morbidity and mortality worldwide, especially among young adults. About 2.5 million people in the United States are treated in the hospital for traumatic brain injury (TBI) each year, and around 70,000 Americans die of TBI annually. The most common causes of severe TBI are falls, motor vehicle accidents, and acts of violence. Mortality rates in severe TBI have decreased from 50% to about 25% over the last three decades, emphasizing the impact of improvements in medical and surgical management. Improvements in the treatment and prevention of secondary brain injury, which occur hours to days after the initial trauma, likely account for a substantial fraction of this reduction in mortality.

Initial Stabilization and Management

Initial management focuses on airway, breathing, and circulation. The Glasgow Coma Scale (GCS) is widely used for classification and prognosis (Table 63.1). The GCS consists of an assessment of eye opening/level of consciousness, motor, and verbal responses. According to this scale, head injuries are classified as mild or concussive (GCS, 13-15), moderate (GCS, 9-12), and severe (GCS, 3-8). The patients with GCS score less than or equal to 8 usually require endotracheal intubation and mechanical ventilation. Fluid resuscitation, blood transfusion, and/or vasopressors to maintain adequate perfusion are initiated in cases of ongoing bleeding and hypotension. Because approximately 15% of patients with TBI have

an associated spinal cord injury, an initial effort should be made to stabilize and immobilize the spine (see Chapter 61, Acute Spinal Cord Disorders). Once stabilization has been achieved, computed tomography (CT) of the head and spine should be obtained to assess the magnitude and type of injury. The range of head injuries includes simple scalp lacerations, skull fractures, cerebral contusions, intracranial hemorrhage (epidural, subdural, intraparenchymal, and subarachnoid hemorrhages), vascular injury, and diffuse axonal injury. Emergent neurosurgical consultation is indicated in penetrating TBI, skull fractures, intracranial hematoma, or cerebral hemorrhages, as these may require immediate operative management. Further management of head injury is based on prevention, recognition, and aggressive treatment of secondary injury to the brain. Mechanisms of such injury include hypoxia, hypotension with hypoperfusion, elevated intracranial pressure (ICP), and seizures or status epilepticus, among others.

TABLE 63.1 Glasgow Coma Scale

Best eye opening	
Spontaneous	4
With voice only	3
With pain only	2
None at all	1
Best verbal response	
Coherent speech	5
Confused intelligible speech	4
Inappropriate words	3
Incomprehensible sounds	2

Best eye opening	
No verbal output	1
Best motor response	
Follows commands	6
Localizes pain stimuli[a]	5
Withdraws to pain stimuli	4
Decorticate posturing	3
Decerebrate posturing	2
No movements at all	1

[a]Localizing pain stimuli refers to gaze deviation, head turning, or hand movements toward the stimulus.

Intensive Care Unit Management of Patients With Severe Traumatic Brain Injury

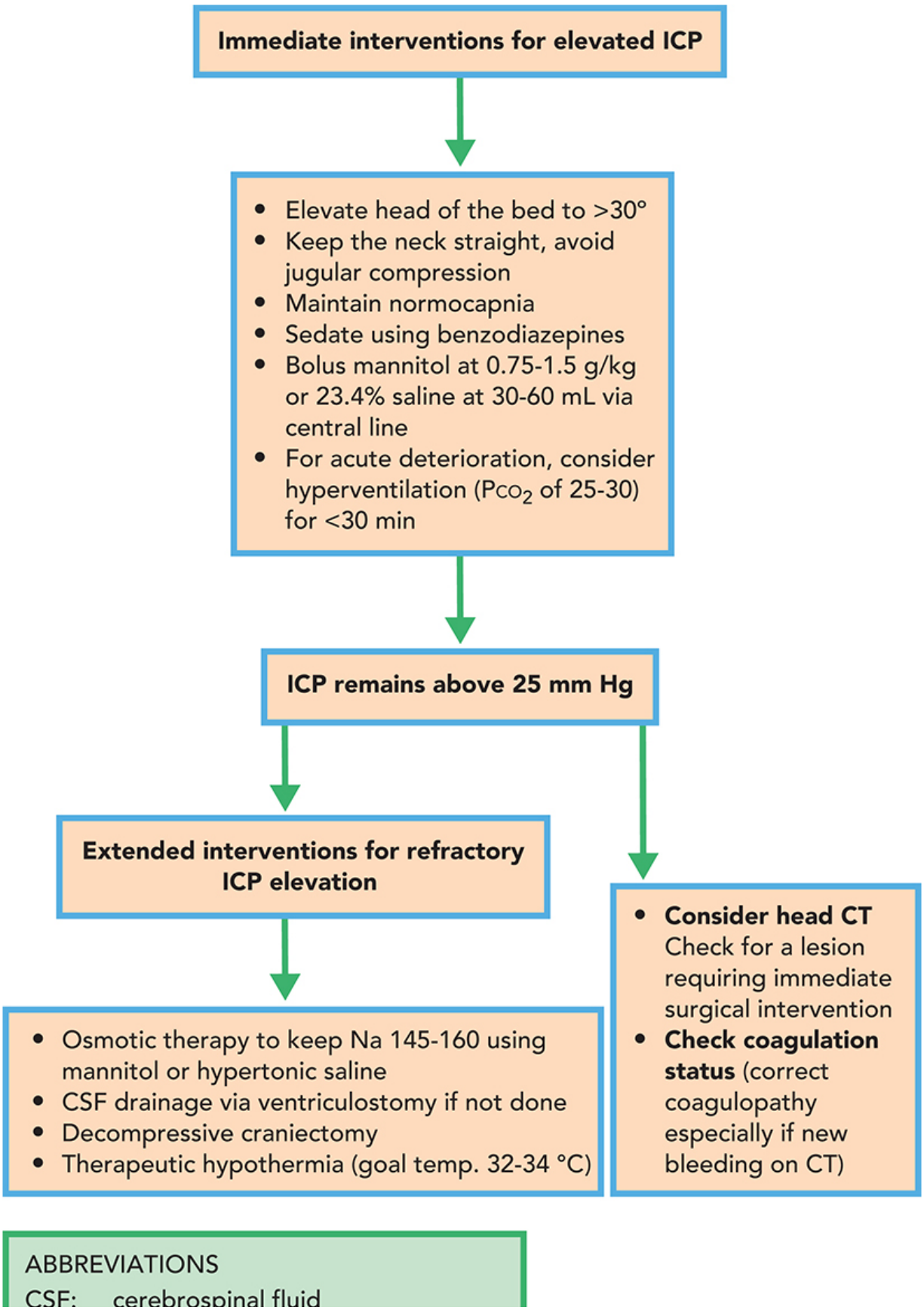
Once stabilized, patients with severe TBI should be monitored in an intensive care unit (ICU) with ICP- and cerebral perfusion pressure (CPP)-monitoring capabilities. CPP is the difference between mean arterial pressure (MAP) and ICP. MAP is most accurately measured by direct arterial cannulation (eg, radial, femoral). ICP/CPP monitoring is indicated in all cases of severe TBI (GCS ≤8) with clinical or radiologic suspicion of current or impending elevated ICP, and/or an inability to reliably detect reduced cerebral perfusion without ICP monitoring. ICP can be measured using either a ventricular catheter (which has the advantage of allowing cerebrospinal fluid [CSF] drainage) or a parenchymal fiberoptic probe (which has the advantage of continuous ICP monitoring).

Routine ventricular catheter exchange and prophylactic antibiotic use for ventricular catheter placement are not recommended.

Intracranial Pressure Control

Elevated ICP (>20 mm Hg) after head injury is associated with unfavorable outcomes. In approximately half of those who die after severe TBI, increased ICP with herniation is the primary cause of death. In all patients who have ICP monitors, universal measures should be instituted, including elevating the head of the bed to 30°, keeping the chin midline to avoid jugular compression, maintaining normocarbia, normothermia, and euvolemia, and avoiding hyponatremia. For refractory ICPs (>20 mm Hg for >5 minutes), sedation, osmotherapy, hyperventilation, hypothermia, and surgical decompression should be considered (Algorithm 63.1). Hyperventilation is not recommended for the management of elevated ICP, because it results in intracranial vasoconstriction, therefore worsening cerebral perfusion. It is reserved only as a brief temporizing measure for acute symptoms of herniation while more definitive interventions are arranged.

ALGORITHM 63.1 **Management of Elevated ICP**


Immediate interventions for elevated ICP
Elevate head of the bed to >30°
Keep the neck straight, avoid jugular compression
Maintain normocapnia
Sedate using benzodiazepines
Bolus mannitol at 0.75-1.5 g/kg or 23.4% saline at 30-60 mL via central line
For acute deterioration, consider hyperventilation (P_{CO_2} of 25-30) for <30 min
ICP remains above 25 mm Hg
Extended interventions for refractory ICP elevation
Osmotic therapy to keep Na 145-160 using mannitol or hypertonic saline
CSF drainage via ventriculostomy if not done
Decompressive craniectomy
Therapeutic hypothermia (goal temp. 32-34 °C)
Consider head CT Check for a lesion requiring immediate surgical intervention
Check coagulation status (correct coagulopathy especially if new bleeding on CT)
ABBREVIATIONS
CSF: cerebrospinal fluid

CT: computed tomography
ICP: intracranial pressure
P_{CO_2}: partial pressure of carbon dioxide

Cerebral Perfusion Pressure Threshold

Maintenance of CPP at 60 to 70 mm Hg is generally necessary following severe TBI to maintain adequate cerebral blood flow; any reduction below these levels increases the risk for cerebral ischemia. CPP may drop because of a decrease in MAP, an increase in ICP, or a combination of these mechanisms. Maintenance of CPP is achieved by maintaining euvolemia, avoiding hypotension, controlling elevated ICP, and, in refractory cases, using vasopressors to augment MAP (Table 63.2).

TABLE 63.2 Cerebral Perfusion Pressure Management

Keep systolic blood pressure above 100-110 mm Hg until CPP can be measured.
Use normal saline boluses and vasopressors if needed to avoid hypotension.
Once ICP monitor is inserted, CPP goal is 60-70 mm Hg (CPP = MAP − ICP).
Control ICP (see Algorithm 63.1).
Use vasopressors to augment MAP and CPP in refractory cases.

CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure.

Seizure Prophylaxis

Up to 25% of patients with TBI will experience a posttraumatic seizure within 7 days of injury, thus seizure prevention with anticonvulsants is indicated for 7 days after TBI. Prophylaxis should not extend beyond 1 week as it does not affect the development of late posttraumatic seizures.

Venous Thromboembolism Prevention

Sequential compression devices should be used from admission, and subcutaneous low-molecular-weight heparin or unfractionated heparin for deep vein thrombosis (DVT) prophylaxis can be started 48 hours after documented cessation of bleeding.

Nutritional Support

Metabolic expenditures are higher in patients with severe TBI; therefore, caloric intake should be adjusted to provide approximately 140% of expected requirements. At least 15% of calories should be supplied as protein. Early feeding (within 48-72 hours of insult) is important, resulting in a trend toward fewer infectious complications and lower mortality.

SUGGESTED READINGS

Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury, Fourth Edition. *Neurosurgery*. 2017;80(1):6-15.

For the most up-to-date version of the Brain Trauma Foundation guidelines, visit https://braintrauma.org/coma/guidelines-current

64 Neurologic Approach to Central Nervous System Infections

Sama Astani and Baback Arshi

Central nervous system (CNS) infections can progress rapidly from onset to life-threatening in a matter of hours; therefore, any suspicion should prompt rapid evaluation and treatment. The classic triad of headache, fever, and meningismus may only be seen in half of patients with bacterial meningitis and only some will have focal neurologic deficits and peripheral leukocytosis. The index of suspicion is even higher in immunocompromised patients as any one of these symptoms may be the sole manifestation of infection. In addition to the devastation caused by the infection, complications like abscess formation, hydrocephalus, cerebral infarcts, and seizures may supervene. In addition, neurosurgical procedures, indwelling hardware, and penetrating skull injuries may further complicate the treatment of meningitis.

General Measures

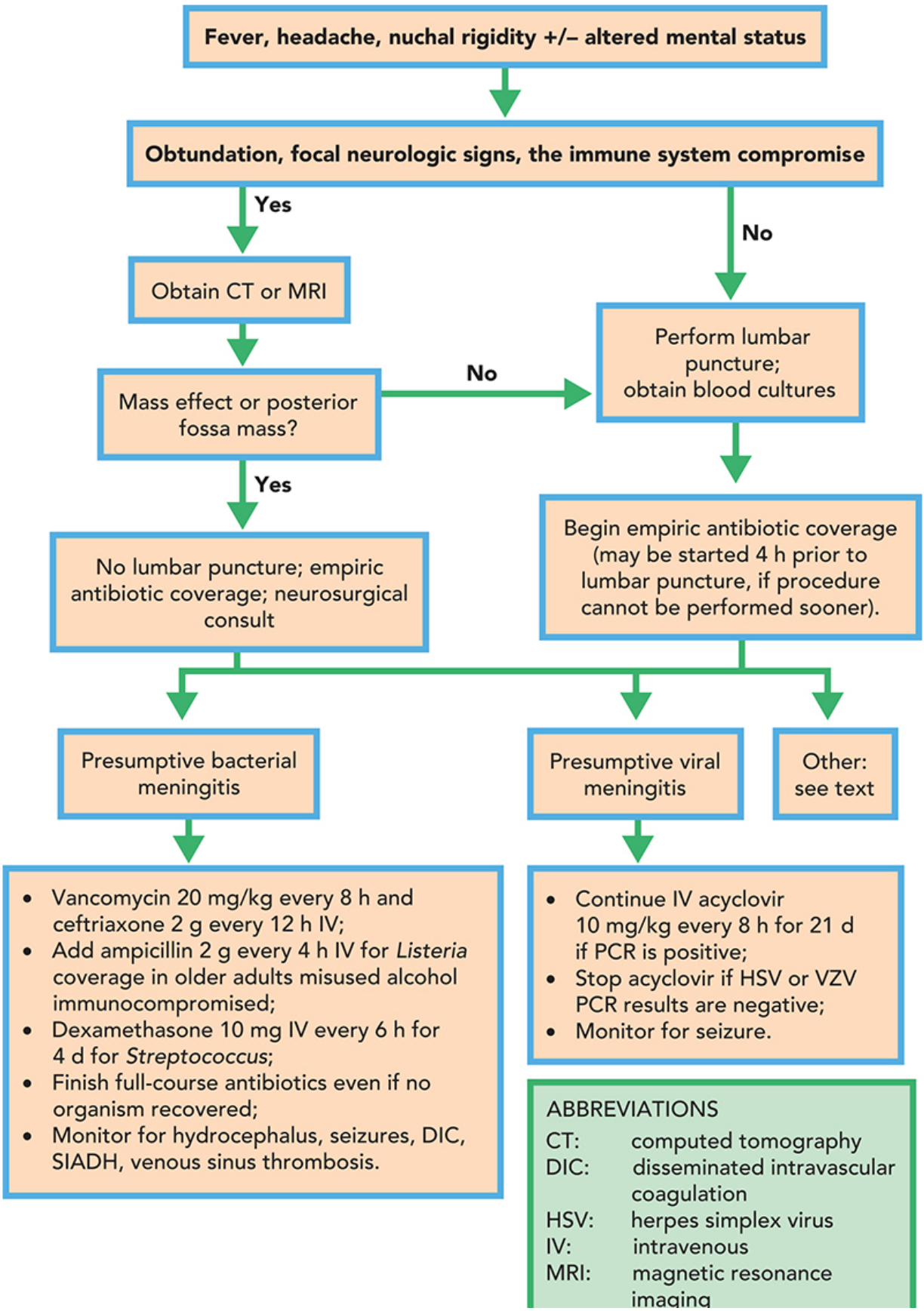
Blood cultures and a lumbar puncture (LP) should be promptly obtained. Those who are immunocompromised or have clinical findings of impaired consciousness, papilledema, or focal neurologic deficits should undergo brain imaging prior to LP due to the risk of herniation from a mass lesion (Table 64.1). Correction of any coagulopathy should be done prior to LP to prevent the development of a spinal epidural hematoma. Opening pressure should always be measured and the standard lab profile should be sent as shown in Table 64.2. Treatment with antimicrobials should not be delayed by LP, although antimicrobials may reduce the yield of cerebrospinal

fluid (CSF) cultures if started prior to LP; a Gram stain may still provide positive results. Treatment should be appropriate for age and other risk factors and should remain broad until the pathologic organism is isolated (Algorithm 64.1). Current data suggest improved neurologic outcomes with early initiation of dexamethasone when given before or during the first dose of antibiotics for *Streptococcus pneumoniae* meningitis. It is useful to save CSF for future studies. Once results of cell count, protein, and glucose are obtained, they could suggest an infection caused by a likely class of organisms and therefore extra agglutination or polymerase chain reaction (PCR) testing might be warranted. Table 64.2 lists the various CSF patterns according to cause.

TABLE 64.1 Contraindications to Lumbar Puncture

Absolute	Relative
Space-occupying lesion in the posterior fossa Presence of midline shift Effacement of basal cisterns or fourth ventricle Skin infection in the area of puncture Lumbar epidural abscess or empyema	International normalized ratio >1.6 Platelet count <50,000/mcL

ALGORITHM 64.1 Approach to Treatment of Suspected Infection of the Central Nervous System


Fever, headache, nuchal rigidity +/– altered mental status
Obtundation, focal neurologic signs, the immune system compromise
Yes
No
Obtain CT or MRI
Perform lumbar puncture; obtain blood cultures
Mass effect or posterior fossa mass?
No
Yes
No lumbar puncture; empiric antibiotic coverage; neurosurgical consult
Begin empiric antibiotic coverage (may be started 4 h prior to lumbar puncture, if procedure cannot be performed sooner).
Presumptive bacterial meningitis
Presumptive viral meningitis
Other: see text
• Vancomycin 20 mg/kg every 8 h and ceftriaxone 2 g every 12 h IV;
• Add ampicillin 2 g every 4 h IV for Listeria coverage in older adults misused alcohol immunocompromised;
• Dexamethasone 10 mg IV every 6 h for 4 d for Streptococcus;
• Finish full-course antibiotics even if no organism recovered;
• Monitor for hydrocephalus, seizures, DIC, SIADH, venous sinus thrombosis.
• Continue IV acyclovir 10 mg/kg every 8 h for 21 d if PCR is positive;
• Stop acyclovir if HSV or VZV PCR results are negative;
• Monitor for seizure.
ABBREVIATIONS
CT: computed tomography
DIC: disseminated intravascular coagulation
HSV: herpes simplex virus
IV: intravenous
MRI: magnetic resonance imaging

PCR: polymerase chain reaction
SIADH: syndrome of inappropriate antidiuretic hormone secretion
VZV: varicella-zoster virus

TABLE 64.2 CSF Findings Suggestive of Infection

CSF Parameter	Bacterial Meningitis	Viral Meningitis	Fungal Meningitis
Opening pressure (cm H_2O)	>18	9-18	>18
White cell count	100-10,000	5-1,000	5-1,000
Percent neutrophils	>80	<20	<20
Protein	100-500	<100	>100
Glucose	<40	>40	<40
Gram stain (% positive)	60-90	0	0
Culture (% positive)	70-85	50	25-50

CSF, cerebrospinal fluid.

Meningitis

In general, meningitis is the most common type of CNS infection, with mortality reaching 60% in bacterial meningitis. Delays in diagnosis and timely antimicrobial treatment can be catastrophic.

BACTERIAL MENINGITIS

An accurate history may elucidate the source and allow a more narrow differential diagnosis. The classical presentation of bacterial

meningitis includes either a stiff neck due to meningeal irritation, headache, fever, and changes in mental status. It is notable that patients may not have all the physical exam findings. Common organisms in the adult population include *S. pneumoniae* (most common in adults), *Neisseria meningitidis, Haemophilus influenzae*, and *Staphylococcus aureus.* In the older adults, chronic alcoholics, or immunocompromised patients, *Listeria monocytogenes* should be considered. Those with neurosurgical hardware or penetrating skull injuries should also be covered for aerobic gram-negative bacilli and methicillin-resistant *Staphylococcus*.

The Infectious Disease Society of America (IDSA) recommend initial empiric antibiotics, including ceftriaxone (or meropenem) and vancomycin. If *Listeria* is suspected, ampicillin should be added to the initial regimen of antibiotics. Patients should be monitored closely for complications, including septic shock, cerebral edema, hydrocephalus, cerebral venous sinus thrombosis, seizures, disseminated intravascular coagulation, hearing loss, and syndrome of inappropriate antidiuretic hormone secretion. Often neurologic consultation is valuable not only for help in diagnosis and treatment but also for identification of associated neurologic complications.

ASEPTIC MENINGITIS

Aseptic meningitis refers to inflammation of the meninges without an isolated bacterium in the CSF. Etiologies range from infectious to noninfectious. Infectious aseptic meningitis could occur in the setting of varied viruses, syphilis, Lyme disease, Rocky Mountain spotted fever, HIV, and West Nile virus. The incidence of viral meningitides is higher than that of bacterial meningitides. While the presentation is like that of bacterial meningitis including headache, fever, meningismus, and photophobia, patients usually have a less toxic appearance, and sensorium is less likely to be altered. Most cases of aseptic meningitis are self-limited and carry a favorable outcome. If microbiologic tests yield negative results and there is no clinical improvement with antibiotics, consider noninfectious causes of

meningitis (Table 64.3). CSF cytology with flow cytometry should be requested if malignancy is suspected.

TABLE 64.3 Causes of Aseptic Meningitis

- Medications and toxins
  Nonsteroidal anti-inflammatory medications (ibuprofen, ketorolac)
  Chemotherapy agents (especially intrathecal preparations)
  Antibiotics (metronidazole, trimethoprim-sulfamethoxazole, isoniazid)
  Vaccinations
  Intravenous immunoglobulin G
  Intravenous contrast
- Neoplastic (leptomeningeal metastases)
- Autoimmune or inflammatory disorders
  Systemic lupus erythematosus
  Sjögren syndrome
  Primary central nervous system angiitis
  Behçet disease

Encephalitis

Encephalitis occurs when there is infection/inflammation of brain parenchyma. Cerebral dysfunction is the key trait that differentiates encephalitis from meningitis. This can be characterized by altered mental status, motor or sensory deficits, personality changes, movement disorders, aphasia, or psychiatric symptoms such as hallucinations, delusions, and paranoia. In common practice, many patients will exhibit signs of parenchymal and meningeal inflammation, and should more appropriately be diagnosed as having a meningoencephalitis.

HERPES SIMPLEX VIRUS ENCEPHALITIS

Herpes simplex virus (HSV) encephalitis is known for not only its high morbidity and mortality, but also its responsiveness to timely institution of antiviral therapy. Common presentation includes fever and altered mental status. Other presenting signs may include focal neurologic findings such as hemiparesis, aphasia, ataxia, or focal seizures. CSF is usually hemorrhagic with a moderate lymphocytic pleocytosis and elevated protein. Patients suspected of having HSV encephalitis should be started on acyclovir until HSV PCR is confirmed negative. Electroencephalogram (EEG) performed in the setting of HSV encephalitis can show focal slowing or epileptiform activity, typically over the temporal lobes. Hemorrhagic lesions on head computed tomography (CT) or brain magnetic resonance imaging (MRI) may be present in the subacute or chronic phase of the disease or if treatment is not initiated promptly. Prompt diagnosis and timely treatment of this infection is of paramount importance given its significant morbidity and mortality; acyclovir should be given intravenously (IV) for the entire duration of treatment. Mortality approaches 70% in untreated cases.

VARICELLA-ZOSTER VIRUS ENCEPHALITIS

Behind HSV encephalitis, varicella-zoster virus (VZV) is one of the most common sporadic viral encephalitis in the world. Typically, VZV presents with a painful, dermatomal rash prior to neurologic involvement, but can notably be absent in some cases, and usually presents in patients as a reactivation in older patients or patients who are immunocompromised. Patients can present with focal neurologic deficits, altered consciousness, cranial neuropathies, seizures, aphasia, and weakness. In additional, VZV can cause a vasculopathy of large and small cerebral arteries that can cause ischemic stroke or intracerebral hemorrhage. Treatment should be prompt with IV acyclovir.

ARTHROPOD-BORNE ENCEPHALITIS

This class of viral encephalitides is typically spread via mosquito or tick. They include St. Louis encephalitis, California encephalitis, Japanese B encephalitis, Eastern and Western equine encephalitis, and West Nile encephalitis. West Nile virus is the most common viral encephalitis in the United States. It can present with systemic symptoms such as fever, myalgias, and rash, but in a small number of people, it can manifest serious neurologic sequelae including flaccid quadriparesis, encephalopathy, movement disorders, and death. CSF analysis would reveal immunoglobulin M (IgM) titers against West Nile virus. Treatment of this class of infection is generally supportive.

Brain Abscess

Brain abscess, subdural empyema, and epidural abscess represent a subset of less frequently seen CNS infections. Patients typically present with focal neurologic deficits. Brain abscess arises from one of three sources: direct spread (such as from an infected sinus), hematogenous spread from another source (eg, pneumonia, endocarditis), or penetrating trauma. Similarly, subdural and epidural abscesses develop from direct spread or after surgical manipulation. The presentation of a brain abscess typically involves headache lateralizing to the side of the abscess accompanied by focal neurologic signs. Evidence of elevated intracranial pressure (papilledema, vomiting, or depressed level of consciousness) may also be present. Diagnosis relies primarily on neuroimaging with a contrast agent. The typical abscess appears as a ring-enhancing lesion with surrounding edema. Abscesses resulting from hematogenous spread (septic emboli due to endocarditis) may present as multiple lesions. In case of endocarditis, patients should undergo cerebral vascular imaging to evaluate for mycotic aneurysms. Subdural empyema and epidural abscess are classified as neurosurgical emergencies. LP should not be performed when signs of elevated intracranial pressure are present.

The workup for the source should include blood and urine cultures, echocardiography, and possibly further body imaging. Toxoplasma titers are checked in immunocompromised patients. Antimicrobial coverage for brain abscesses varies with the presumptive source of infection. Empiric treatment in patients without prior surgical manipulation should include vancomycin, metronidazole, and a third-generation cephalosporin (ceftriaxone or ceftazidime). For patients who are immunocompromised or who have had surgical manipulation, consider the use of a fourth-generation cephalosporin, such as cefepime, to further target *Pseudomonas*. Prompt neurosurgical consultation should be rendered if intracranial abscess is seen. In some, abscesses can be solely managed with antimicrobial agents; however, surgical intervention can be considered in some situations such as patients with risk of ventricular extension or patients who may be candidates for stereotactic aspiration.

Neurosurgical patients are at risk in the months or even years after a procedure. Most brain abscesses are bacterial and sometimes polymicrobial. Common aerobes include *Streptococcus* species, *Staphylococcus* species (especially after surgical procedures), *Pseudomonas* species, and *Enterobacter* species (otitis media). Anaerobic abscesses (*Bacteroides* and *Actinomyces* species) may arise from oral sources (dental carries) and abdominal or pelvic infections. Patients with neutropenia and individuals who have received transplants have a particular predilection for *Aspergillus* abscesses. Toxoplasmosis is the most common intracranial infection in patients with acquired immunodeficiency syndrome (AIDS).

Infections Related to Neurosurgery

Infections following neurosurgery include meningitis, encephalitis, ventriculitis, abscess, and hardware infection. These typically occur within weeks of surgery, although vulnerability to infections remains for years. Ventriculoperitoneal shunt infections may present with symptoms of hydrocephalus (eg, increasing headaches, vomiting,

lethargy) or abdominal distention; otherwise, symptoms are similar to other types of CNS infections. Shunts are assessed with imaging to determine their functional status and tapped to sample CSF and identify the organism. Infected hardware should be removed if possible. The most common organisms causing postneurosurgical infection include *Staphylococcus* species and gram-negative organisms.

Tropical Central Nervous System Infections

Tuberculous meningitis, West Nile encephalomyelitis, and neurocysticercosis comprise a group of tropical diseases that have become increasingly common in the United States. Tuberculous meningitis carries a high mortality, and presentation includes altered mental status, lethargy, cranial neuropathies, and hemiparesis. West Nile encephalomyelitis, mentioned earlier, is typically encountered in warm-climate months, spread by mosquitos, and causes fever, encephalitis, meningitis, and a polio-like illness presenting with flaccid paralysis. Neurocysticercosis, the world's leading cause of adult-onset seizure, is transmitted by consumption of undercooked pork that contains *Taenia solium* larvae.

Immunocompromised Patients

These include patients with AIDS, individuals who have received solid-organ or bone marrow transplants, and those receiving chemotherapy or immunosuppression for autoimmune conditions. The most common infections include toxoplasmosis, cryptococcal meningitis, fungal abscess (*Aspergillus*), and progressive multifocal leukoencephalopathy (PML) that arises from the presence of John Cunningham (JC) virus. Special CSF testing includes PCR testing for *Toxoplasma*, JC virus, Epstein-Barr virus, and cytomegalovirus, as well as *Cryptococcus* and *Histoplasma* antigen testing. The Venereal Disease Research Laboratory (VDRL) test should also be

requested, given the higher incidence of neurosyphilis in patients with AIDS. An infectious diseases consult is strongly recommended if CNS infection is suspected in an immunocompromised patient.

SUGGESTED READINGS

Tunkel AR, Hasbaun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis.* 2017;64(6):e34-e65.

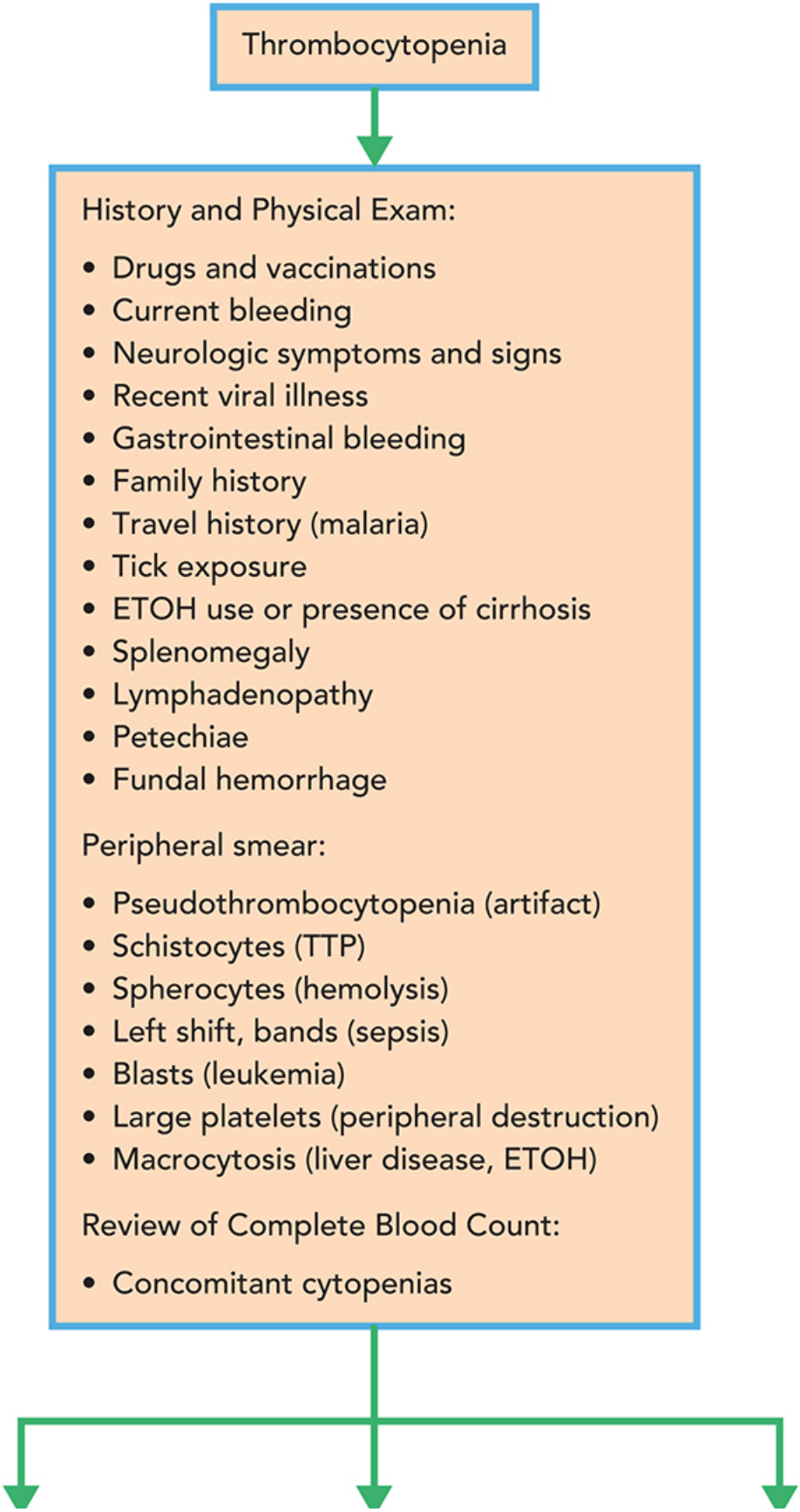
SECTION XV HEMATOPOIETIC DISORDERS

65 Thrombocytopenia in the Intensive Care Unit

Marin H. Kollef

Thrombocytopenia is a very common occurrence in the intensive care unit (ICU), occurring in as many as 60% of patients either before ICU admission or during the course of their ICU stay. A normal platelet count ranges between 150,000 and 450,000/mcL. In the ICU, it is important to recognize that the absolute platelet count is important, but trends in the platelet count, specifically a decline by more than 50% even if still in the normal platelet range, may be evidence of a serious clinical problem such as heparin-induced thrombocytopenia (HIT), which requires urgent attention. A systematic approach to the diagnosis allows for the common causes to be detected early and enables rational use of platelet transfusions (Algorithm 65.1). Platelet survival in the circulation is approximately 7 to 10 days, and one-third of the platelets are sequestered in the spleen under normal circumstances.

ALGORITHM 65.1 **Diagnostic Algorithm for Thrombocytopenia**


Thrombocytopenia
History and Physical Exam:
• Drugs and vaccinations
• Current bleeding
• Neurologic symptoms and signs
• Recent viral illness
• Gastrointestinal bleeding
• Family history
• Travel history (malaria)
• Tick exposure
• ETOH use or presence of cirrhosis
• Splenomegaly
• Lymphadenopathy
• Petechiae
• Fundal hemorrhage
Peripheral smear:
• Pseudothrombocytopenia (artifact)
• Schistocytes (TTP)
• Spherocytes (hemolysis)
• Left shift, bands (sepsis)
• Blasts (leukemia)
• Large platelets (peripheral destruction)
• Macrocytosis (liver disease, ETOH)
Review of Complete Blood Count:
• Concomitant cytopenias

ETOH, alcohol; TTP, thrombocytopenic thrombotic purpura.

Recognition of thrombocytopenia normally occurs after a complete blood count is drawn, but it is important to remember that mucocutaneous bleeding is a classic sign of thrombocytopenia. Bleeding from thrombocytopenia normally occurs only once the platelet count falls below 50,000/mcL in postsurgical patients, while spontaneous bleeding can occur with counts below 5,000/mcL. The diagnostic approach starts with a thorough history and physical examination, followed by examination of the peripheral smear. A pathophysiologic approach to thrombocytopenia enables all common causes to be rapidly screened for and facilitates recognition of potential causes (Table 65.1). Careful attention should be paid to prescription and over-the-counter drugs (Table 65.2).

TABLE 65.1 Pathophysiologic Classification of Thrombocytopenia

Decreased Production	Increased Destruction	Increased Sequestration
Aplastic anemia	Immunologic	Hypersplenism from any cause:
Hematologic malignancies	ITP	
Lymphoma	Heparin-induced (HIT)	Cirrhosis
Leukemia	Drug-induced (see Table 65.2)	Portal hypertension

Decreased Production	Increased Destruction	Increased Sequestration
Myelodysplasia	HIV	Congestive heart failure
Metastatic malignancy	Autoimmune disease	Hematologic malignancies
Nutritional (B_{12} and folate)	Infectious	Lipid storage disorders
Drugs (see Table 65.2)	Posttransfusion purpura	Malaria
Chemotherapy and radiation Alcohol	Antiphospholipid antibody syndrome	Babesiosis
PNH Viral infections	Nonimmunologic	
HIV Mumps Parvovirus Varicella Rubella Epstein-Barr virus Hepatitis C	DIC HUS/TTP HELLP syndrome Preeclampsia/eclampsia Malignant HTN Sepsis Cardiac valves Burns Massive bleeding	

DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzyme levels and a low platelet count; HIT, heparin-induced thrombocytopenia; HIV, human immunodeficiency virus; HTN, hypertension; HUS, hemolytic uremic syndrome; ITP, immune thrombocytopenic purpura; PNH, paroxysmal nocturnal hemoglobinuria; TTP, thrombotic thrombocytopenic purpura.

TABLE 65.2 Common Drugs Associated With Thrombocytopenia

Decreased Production	Immune-Mediated Destruction	Unknown Mechanism
Chemotherapeutic agents Busulfan Cyclophosphamide Cytosine arabinoside Daunorubicin Methotrexate 6-Mercaptopurine Vinca alkaloids Daptomycin Estrogens Ethanol Linezolid Thiazide diuretics	Abciximab (all GP2b3a inhibitors) Amiodarone Amphotericin B Aspirin Atezolizumab Aztreonam Carbamazepine Chloroquine Cimetidine Clopidogrel Digoxin Eptifibatide Heparin Meropenem Phenytoin Piperacillin Quinine Ranitidine Trimethoprim/sulfamethoxazole Vaccine-induced[a] Valproic acid Vancomycin	Fluconazole Ganciclovir Nitrofurantoin Rifampin Valganciclovir

[a]Vaccine-induced caused by COVID-19 vaccines and MMR (measles, mumps, and rubella).

Common causes of thrombocytopenia in an ICU setting include:

- Drug-induced (heparin, H_2-receptor blockers, GP2b3a inhibitors, antibiotics, alcohol)
- Sepsis
- Massive bleeding
- Thrombocytopenia with microangiopathic hemolytic anemia (thrombocytopenic thrombotic purpura [TTP], hemolytic uremic syndrome [HUS], disseminated intravascular coagulation [DIC])

Clinical recognition of the cause is vital as therapies differ considerably depending on the underlying etiology. For example, a patient with thrombocytopenia secondary to bleeding should be treated with platelets, compared with a patient with TTP/HUS, in whom platelet transfusion is generally contraindicated and treatment entails use of plasmapheresis or eculizumab. A few common conditions will be discussed, and readers are encouraged to refer to the “Suggested Readings” section for further details.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is a condition caused by autoantibodies directed against platelet surface glycoproteins, causing increased platelet destruction. ITP should be differentiated from drug-induced thrombocytopenia. ITP is considered primary when not associated with other conditions like systemic lupus erythematosus, chronic lymphocytic leukemia, and selective immunoglobulin deficiency (IgA) or infections such as HIV, hepatitis C, COVID-19, or cytomegalovirus (CMV). Binding of the antibodies results in accelerated platelet removal by the spleen. *Evans syndrome* refers to ITP together with autoimmune hemolytic anemia. The diagnosis of ITP is made by exclusion; checking for antiplatelet antibodies has no role in the diagnosis. Treatment consists of corticosteroids, intravenous immunoglobulin (IVIG), anti-RhD antibodies, rituximab, danazol, cyclophosphamide, azathioprine, or splenectomy, as well as platelet transfusions, tranexamic acid, and aminocaproic acid for severe bleeding.

Heparin-Induced Thrombocytopenia

Type 1 HIT: Platelet counts often decline modestly in the first few days after starting therapy with a heparin product. This is a spontaneously resolving, reversible decline with a platelet nadir

above 100,000/mcL. This condition is not normally associated with complications.

Type 2 HIT: This is a much more serious disorder that occurs when patients develop antibodies against the heparin-platelet factor-4 complex. It can be induced by exposure to unfractionated or low-molecular-weight heparins. Important clues to the diagnosis include a greater than 50% decline in the platelet count 5 to 10 days after being exposed to heparin for the first time. A more rapid decline in platelet counts can occur with prior heparin exposures. The platelet count is often well below 100,000/mcL without clinical evidence of bleeding. In addition, patients may develop erythema or necrosis at heparin injection sites and systemic symptoms like fever, wheezing, and tachycardia from heparin boluses. The major clinical problem with continued heparin exposure is not bleeding but devastating thrombotic complications in up to 50% of patients. These thromboses can be venous or arterial and can result in life-threatening complications such as limb ischemia, deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebral sinus thrombosis, stroke, and mesenteric and renal infarction.

The 4Ts score (Table 65.3) quantifies the clinical findings associated with HIT and provides a pretest likelihood for the diagnosis of HIT. When HIT is suspected, all sources of heparin products should be immediately stopped, a serologic test (ELISA) for heparin-dependent antibodies should be requested, and the patient should be started on a direct thrombin inhibitor. The current enzyme-linked immunosorbent assay (ELISA) for heparin-platelet factor-4 antibodies is highly sensitive but has low specificity. A more specific functional assay, which measures platelet degranulation and serotonin release in response to heparin-platelet factor-4 complexes, is available to confirm the diagnosis of HIT. However, therapy with a direct thrombin inhibitor should not be delayed if there is significant clinical concern for HIT. Currently available direct thrombin inhibitors include argatroban (hepatically metabolized) and bivalirudin (renally cleared). Danaparoid (renally cleared, not available in the United States), a parenteral inhibitor of thrombin and factor Xa, and fondaparinux (renally cleared), an inhibitor of factor Xa, can also be

employed. Appropriate dosing of the thrombin and Xa inhibitors is critical to avoid bleeding complications and should be discussed with an ICU pharmacist, taking into account the patient's renal and hepatic function. Additionally, dosing of fondaparinux is weight-based and dependent on renal function. Platelets should not be given to patients with HIT unless there is life-threatening bleeding. Once the platelet count has demonstrated recovery to greater than 100,000/mcL, warfarin therapy should be initiated, and the direct thrombin inhibitor should be continued until therapeutic anticoagulation with warfarin has been achieved. Increasingly, direct oral anticoagulants (eg, apixaban, dabigatran, edoxaban, rivaroxaban) are also being used for anticoagulation in patients with HIT.

TABLE 65.3 Heparin-Induced Thrombocytopenia 4Ts Score

4Ts Score Parameters	
Thrombocytopenia	
• PLT decrease >50% and nadir ≥20,000 and no surgery within past 3 d	2 points
• PLT decrease >50% but surgery within past 3 d or any combination of PLT fall and nadir that does not fit criteria for 2 or 0 points	1 point
• PLT decrease <30% or nadir <10,000	0 points
Timing of thrombocytopenia onset after heparin exposure	
• 5-10 d or 1 d if exposure within past 5-30 d	2 points
• 5-10 d but missing PLT counts or >10 d or ≤1 d if exposure within past 31-100 d	1 point

4Ts Score Parameters	
• ≤4 d without exposure in the past 100 d	0 points
Thrombosis or other clinical sequelae	
• Confirmed new arterial or venous thrombosis, skin necrosis, anaphylactoid reaction, or adrenal hemorrhage	2 points
• Suspected, progressive, or recurrent thrombosis, skin erythema at heparin injections site	1 point
• None	0 points
Other cause for thrombocytopenia	
• No alternative causes	2 points
• Possible other causes: sepsis	1 point
• Probable other causes: sepsis, DIC, drug-induced, within 72 h of surgery	0 points
Interpretation	
0-3 points	Low probability (risk of HIT <1%)
4-5 points	Intermediate probability (risk of HIT ≅ 10%)
6-8 points	High probability (risk of HIT ≅ 50%)

DIC, disseminated intravascular coagulation; HIT, heparin-induced thrombocytopenia; PLT, platelet.

Sepsis-Induced Thrombocytopenia

Sepsis-induced thrombocytopenia is usually multifactorial and caused by marrow suppression, increased platelet destruction, drugs used to treat the septic patient, and associated DIC. Treatment is supportive, and possible offending drugs should be stopped. Specific infections tend to cause thrombocytopenia, and physicians should be aware of the common culprits, according to their geographic location. In Missouri, ehrlichiosis should to be considered, and travelers from endemic areas should be screened for malaria. DIC is characterized by a combination of microvascular thrombosis and bleeding, thrombocytopenia, coagulopathy, and low fibrinogen levels. Treatment for this complication is supportive, with therapy directed at the underlying cause and occasional use of platelets, fresh frozen plasma, and cryoprecipitate for the actively bleeding patients.

Thrombotic Thrombocytopenic Purpura

The diagnostic pentad of TTP include:

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Renal failure
- Fever
- Altered mental status

However, all five criteria are met in less than 40% of patients. The major differential diagnosis is DIC. Both TTP and DIC are associated with thrombocytopenia, microangiopathic hemolytic anemia, and schistocytes. In DIC, there is often an associated coagulopathy with prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time, which should all be normal in TTP. In addition, fibrinogen levels in DIC are low, and fibrin degradation product (FDP) levels are high, which should not be seen in TTP. The

degree of thrombocytopenia is often more severe in TTP compared to DIC, and the associated elevation in lactate dehydrogenase (LDH) levels is also more profound.

Management of patients with TTP is challenging. Importantly, platelet transfusions in these patients are contraindicated in the absence of life-threatening bleeding as they can precipitate vasoocclusive crises of vital organs, such as the brain and myocardium. This disorder is caused by an acquired deficiency of ADAMTS13, which normally cleaves von Willebrand factor multimers. Absence of ADAMTS13 activity results in large circulating multimers of von Willebrand factor, which cause platelets to adhere to the endothelium with resultant thrombosis, thrombocytopenia, and shearing of red cells as they pass the thrombi. Thus, the patient develops a microangiopathic hemolytic anemia. The syndrome is most commonly precipitated by infections (*Escherichia coli* O157:H7 enteritis, human immunodeficiency virus) or drugs (ticlopidine, cyclosporine, tacrolimus, clopidogrel, immune checkpoint inhibitors, COVID-19 vaccines). Treatment consists of plasma exchange or fresh frozen plasma/intravenous immunoglobulin if plasma exchange is not immediately available. Other medical therapies include glucocorticoids, rituximab, and caplacizumab. The assay for ADAMTS13 plays no role in diagnosis in the acute setting and should not delay therapy.

Vaccine-Induced Immune Thrombotic Thrombocytopenia

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is caused by antibodies that recognize platelet factor 4 (PF4, also called CXCL4) bound to platelets. It was recognized to occur in early 2021 as a prothrombotic syndrome following administration of the AstraZeneca and Johnson & Johnson adenoviral vector COVID-19 vaccines. Therapy includes anticoagulation with a direct oral

anticoagulant (DOAC), fondaparinux, danaparoid, argatroban, or bivalirudin. IVIG and plasma exchange have also been employed.

Platelet Transfusions

The indications for transfusing platelets depend on the cause of the thrombocytopenia and the presence of bleeding. As noted, transfusions should be avoided in TTP and HIT unless the patient is experiencing life-threatening bleeding. For other causes, platelets should be transfused prophylactically when the platelet count is less than 10,000/mcL to prevent spontaneous intracranial bleeding. For major surgery, the counts should be more than 100,000/mcL; for minor procedures, the counts should be more than 50,000/mcL.

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66 Acute Management of the Bleeding Patient/Coagulopathy

Joshua I. Siner and Kristen M. Sanfilippo

Major bleeding in the intensive care unit (ICU) is a common clinical dilemma with management dependent on the underlying etiology. Initial evaluation of the patient by history and physical examination can guide diagnostic work up and in some cases, establish an etiology. Bleeding from a single site is most likely due to an underlying structural defect (eg, site of trauma and surgical wound), whereas a patient bleeding from multiple mucosal surfaces or from puncture sites is likely to have a derangement in the coagulation or fibrinolytic systems of hemostasis (eg, disseminated intravascular coagulation [DIC] and factor deficiency). The absence of a bleeding history suggests an acquired reason for bleeding, whereas a lifelong history of bleeding suggests a genetic or congenital etiology. Determining the cause of bleeding in the patient is paramount to rapid management and control of the bleeding, and it may be difficult to ascertain if a limited history is available.

Hemostasis is a tightly regulated process that involves complex interactions between circulating proteins, blood cells, and vascular endothelial cells. This process can be divided into two phases: *primary* and *secondary hemostasis*. *Primary hemostasis* consists of interactions between intact platelets, endothelial cells, and von Willebrand factor (vWF), which leads to the formation of a primary hemostatic plug. Abnormal primary hemostasis typically results in bleeding from mucosal surfaces (eg, epistaxis, gingival bleeding, gastrointestinal bleeding, or vaginal bleeding) and skin (eg, petechiae or prolonged bleeding at venipuncture sites). *Secondary hemostasis* refers to the formation of the fibrin clot and is achieved through the activation of coagulation proteins. Any significant

deficiency in coagulation proteins or interference with their activations, and hence the formation of the fibrin clot, will lead to excessive bleeding. Abnormal secondary hemostasis may be clinically manifested by spontaneous bleeding from deep tissue sites (eg, intraperitoneal bleeding, hemarthroses, and intramuscular hematomas). This chapter focuses on the identification and management of bleeding, that is, primarily due to abnormalities in secondary hemostasis. Thrombocytopenia-related bleeding and structural bleeding (eg, gastrointestinal bleeding) are addressed elsewhere in this text.

Coagulation

Coagulation and subsequent fibrin formation have been historically represented as occurring by two distinct pathways (Figure 66.1). The extrinsic or tissue factor (TF) pathway is classically triggered by tissue injury and the release of TF into circulation, which then activates factor VII. The intrinsic pathway or contact activation pathway classically occurs in response to blood contact with an artificial or negatively charged surface. Each pathway is depicted as the sequential activation of coagulation factors in the presence of calcium and phospholipids and converges onto a common pathway to form thrombin. Thrombin, in turn, cleaves fibrinogen to form fibrin, and thus a clot is formed. These pathways do not act independently *in vivo*, but this concept is useful in laboratory diagnosis and treatment of coagulopathies; defects in the extrinsic pathway are measured by the prothrombin time (PT) and defects in the intrinsic pathway by the activated partial thromboplastin time (aPTT).

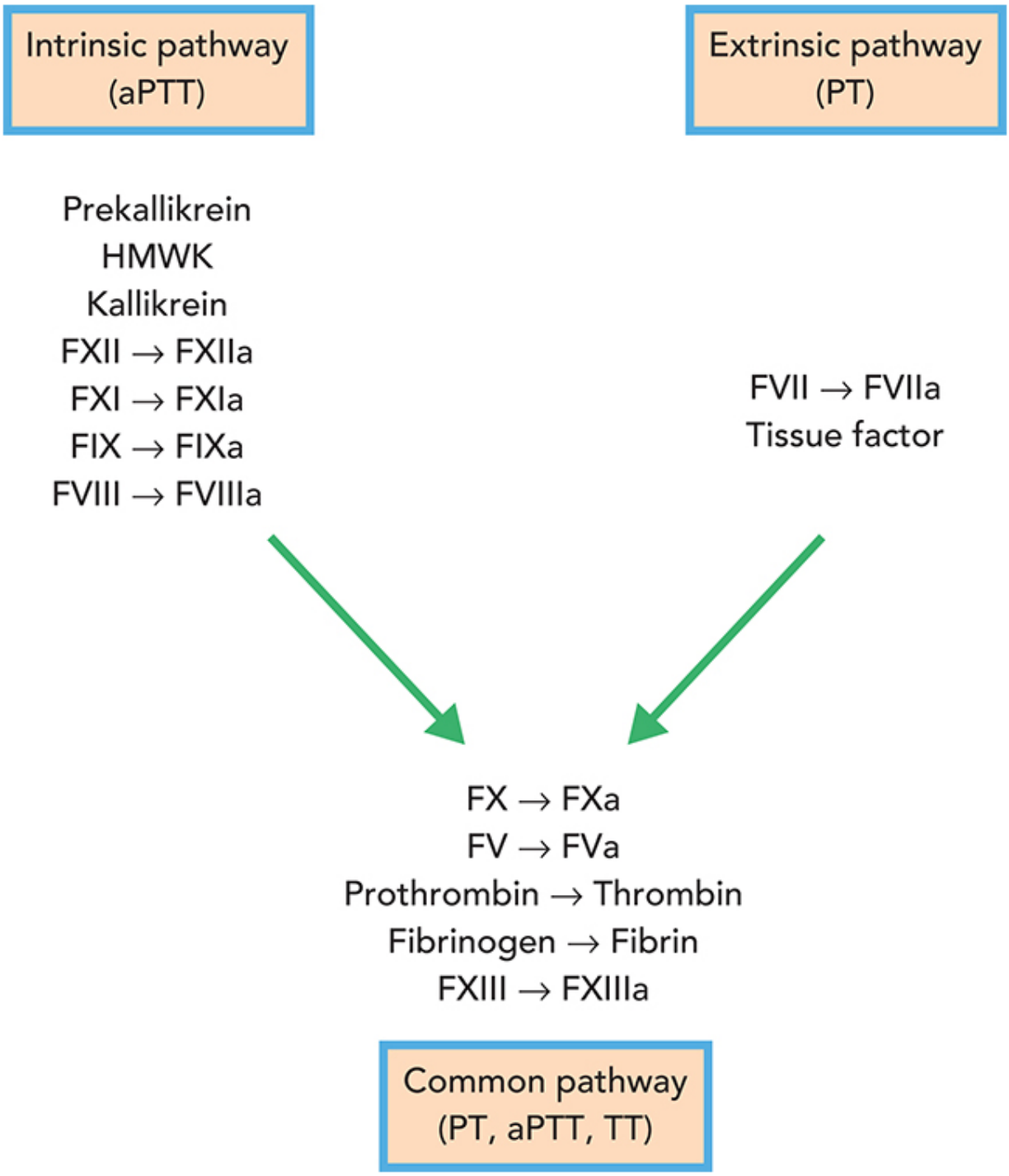

FIGURE 66.1 **Classical model of hemostasis**. The classical coagulation cascade is depicted as two distinct pathways converging on a common pathway. Although the pathways are not distinct in vivo, the distinct pathways can be measured in vitro. Disorders of the intrinsic pathway are measured by the aPTT, and disorders of the extrinsic pathway are measured by the PT. aPTT, activated partial thromboplastin time; FV/FVII/FVIII/FIX/FX/FXI/FXII,

factors V/VII/VIII/IX/X/XI/XII; HMWK, high-molecular-weight kininogen; PT, prothrombin time; TT, thrombin time.

A cell-based model of thrombin generation has been proposed to unify the *in vivo* interaction between the classical pathways in the setting of platelet activation. For coagulation, this model proposes that the TF pathway initiates activation, whereas the contact activation pathway amplifies the activation through factor XI.

SCREENING TESTS FOR COAGULATION

Initial testing to determine the cause of bleeding should include a PT, aPTT, and platelet count. If these fail to elucidate the cause of bleeding, further testing for platelet function and deficiencies in the fibrinolytic pathway may be necessary. Table 66.1 lists the interpretation of the most common patterns of coagulation screening tests.

TABLE 66.1 Rapid Interpretations of Abnormal Prothrombin Time and Activated Partial Thromboplastin Time in a Bleeding Patient

PT Result	aPTT Result	Possible Interpretation and Associating Conditions/Coagulopathy
Normal	Normal	Platelet dysfunction, thrombocytopenia, factor XIII deficiency, alpha-2-antiplasmin deficiency, plasminogen activator inhibitor-1 deficiency
Prolonged	Normal	Liver diseases (early), warfarin therapy, factor VII deficiency/defect
Normal	*Prolonged*	Heparin therapy, hemophilia A/B, factor XI deficiency, factor XII deficiency, lupus anticoagulant[a]

PT Result	aPTT Result	Possible Interpretation and Associating Conditions/Coagulopathy
Prolonged	*Prolonged*	Liver disease (end stage), vitamin K deficiency, oral anticoagulants, disseminated intravascular coagulopathy, isolated fibrinogen, factor II, V, or X deficiency/defect

[a]Although factor XII deficiency and lupus anticoagulant may cause an isolated prolonged aPTT, they are not associated with bleeding.

aPTT, activated partial thromboplastin time; PT, prothrombin time.

FURTHER TESTS TO ASSESS ACUTE BLEEDING

Thrombin Time **(*TT*):** It measures the conversion of fibrinogen to fibrin. Prolonged results occur when

- heparin or a direct thrombin inhibitor is in the test system,
- fibrinogen is decreased or abnormal,
- therapeutic fibrinolysis or fibrinogen degradation products (FDPs) are present, and
- liver disease is severe.

Mixing Studies**:** These studies are conducted to determine the cause of a prolonged aPTT or PT. These tests are performed to distinguish between factor deficiencies and inhibitors of coagulation. A 50:50 mix of the patient's plasma and pooled normal plasma is tested immediately and after 1-hour incubation at 37 °C. Figure 66.2 depicts the interpretation of mixing studies.

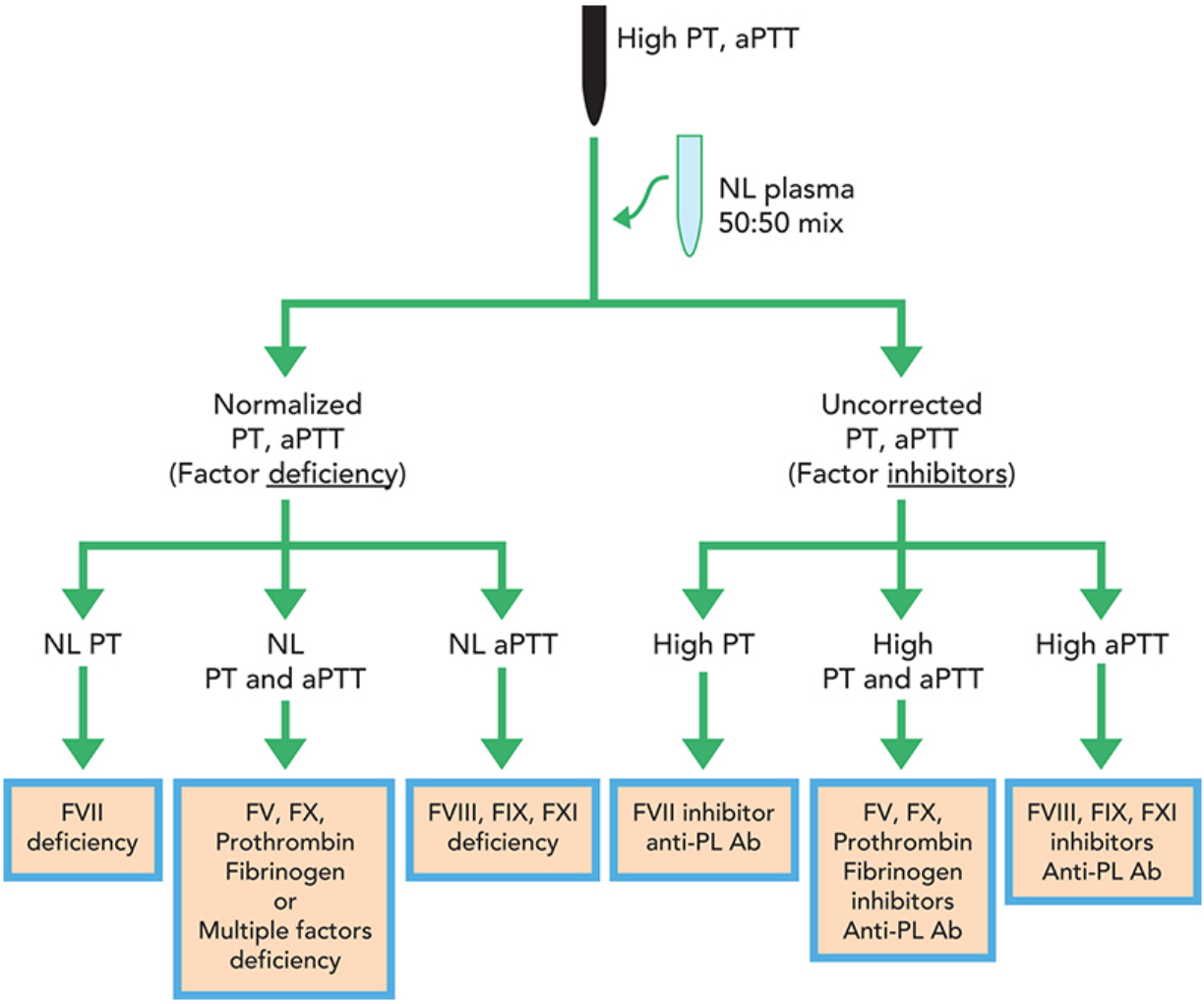

FIGURE 66.2 **Mixing analysis of elevated PT and aPTT in a bleeding patient.** Patient's plasma is mixed with normal pooled plasma at 1:1 ratio, followed by subsequent retesting of PT and aPTT. Normalization of PT or aPTT suggests a factor deficiency. However, if mixing study does not correct the prolongation, this favors the presence of factor-specific or nonspecific inhibitors. anti-PL Ab, antiphospholipid antibody; aPTT, activated partial thromboplastin time; FV/FVII/FVIII/FIX/FX/FXI, factors V/VII/VIII/IX/X/XI; NL, normal; PT, prothrombin time.

Platelet Function Test **(eg, Platelet Function Analyzer-100, PFA-100):** In the presence of a normal platelet count and a hemoglobin level of at least 10 g/dL, PFA-100 is useful in detecting platelet dysfunction, including inherited defects such as von Willebrand disease (vWD) and acquired defects due to aspirin

therapy. Further laboratory testing such as platelet aggregation tests may be needed to characterize the platelet defect but will not alter the initial therapy.

Viscoelastic Tests of Coagulation: Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) are two systems that allow near real-time hemostasis evaluation within 10 to 30 minutes from blood draw. Both devices measure the changes in the physical properties of the clot by monitoring the movement of a pin suspended in activated blood. As the clot begins to form, its physical properties, including elasticity and shear modulus, are displayed on the tracing, giving physicians information on global hemostatic properties during complicated surgical procedures and trauma. Both coagulation pathways (intrinsic or extrinsic) as well as a thrombin time can be simulated depending on the choice of the activator and may be used to monitor heparin effects with the addition of heparinase.

Common Acquired Disorders of Coagulation in the Critical Care Setting

LIVER DISEASE

Causes

- Shock liver due to hypoperfusion
- Acute hepatitis
- Chronic liver disease
- Acute liver injury

Pathophysiology

The liver is the site of production of all coagulation factors including fibrinogen, thrombin, and factors VII, IX, XI, V, and X (except vWF and factor VIII) and fibrinolytic proteins. Thus, hepatic impairment can lead to both a deficiency and an alteration in these liver-

dependent factors and proteins. The liver is also important in clearing activated factors and inhibitors of coagulation. In addition, patients with liver disease, especially chronic, may have associated thrombocytopenia related to a reduction in the production of platelets or due to sequestration from hypersplenism caused by portal hypertension. It is important to recognize that the risk of bleeding in liver disease can vary by the cause and acuity of the liver disease and are related to factor deficiencies, accumulation of activated factors, accumulation of inhibitors of coagulation, and associated thrombocytopenia. Diagnostic workup to identify the hemostatic abnormalities in liver disease guides management.

Diagnosis

Initial workup for the bleeding patient with liver disease should include both tests for primary and secondary hemostasis. These should include platelet levels, PT, aPTT, and fibrinogen. PT and aPTT are often prolonged, and fibrinogen may be low. In liver disease, prolongation of PT can reflect deficiencies of factors VII, V, and X and fibrinogen. Prolongation of aPTT can be due to deficiencies of factors XI, IX, V, and X and fibrinogen attributable to liver disease. Mixing studies for a prolonged PT and aPTT can confirm that the prolongation is due to a factor deficiency as opposed to an inhibitor. In the absence of coagulation factor inhibitors, the abnormal clotting time will be corrected *in vitro* by the 50:50 mixing study. Measuring individual factor levels can identify the deficient ones, and measuring factors V and VII levels may help differentiate liver disease from vitamin K deficiency (both factors are deficient in liver disease, whereas only factor VII is deficient in vitamin K deficiency, and neither are acute phase reactants).

Management

Management of bleeding in liver disease may require the use of blood products to correct the underlying factor deficiencies. Fresh frozen plasma (FFP) contains all of the coagulation factors and protein but at diluted concentrations and thus can require high

volumes and thus pose a risk of volume overload in some patients. Cryoprecipitate is a rich source of fibrinogen, which plays a major role in correcting coagulopathy in liver disease. Finally, platelet transfusions can be considered in the setting of thrombocytopenia and should be based on the severity of bleeding and degree of thrombocytopenia. In general, a PT less than 2 times normal control, a fibrinogen level of greater than 60 mg/dL, and a platelet count 50,000/mcL or more should be adequate to achieve hemostasis. The initial dose of FFP should be 10 to 15 mL/kg (~4-6 units). For patients with thrombocytopenia, 1 unit of single-donor platelets (or 4 units of random platelet concentrates) should be given with a posttransfusion platelet count dictating further dosing. Cryoprecipitate is usually given in pools of up to 10 units, which generally contain 1,500 to 2,000 mg of fibrinogen in 150 mL. In rare cases, where bleeding is not controlled after adequate resuscitation with blood products, recombinant factor VIIa (rFVIIa) might be considered. rFVIIa has been associated with clinically significant thrombosis and should be used with caution. There is no well-defined study for the dosing in off-label use of rFVIIa; however, 20 to 90 mcg/kg should provide adequate hemostatic control. In the absence of active bleeding, prophylactic FFP, cryoprecipitate, or platelet transfusion has not been shown to reduce bleeding risk or improve outcomes and thus should be avoided.

DISSEMINATED INTRAVASCULAR COAGULATION

Cause

DIC is always a symptom of an underlying condition. There are many causes of DIC (Table 66.2). Some of the most common conditions associated with DIC include tissue damage, neoplasia, infection, or obstetric emergencies.

TABLE 66.2 Underlying Conditions Commonly Associated With Disseminated Intravascular Coagulation

Sepsis	Pregnancy complications (abruptio placentae, septic abortion, amniotic fluid embolus, HELLP syndrome, eclampsia, and severe preeclampsia)
Trauma/crush injury	Uterine atony
CNS injury	Fat emboli
Heat stroke	Tumor lysis syndrome
Burns	Acute hemolytic transfusion reaction
Venomous snake bites	Liver disease

CNS, central nervous system; HELLP, hemolysis, elevated liver enzyme levels, and a low platelet count.

Pathophysiology

DIC is a consumptive coagulopathy with rapid and enhanced systemic activation of normal coagulation. Through consumption of coagulation and fibrinolytic factors and their inhibitors, an imbalance in this tightly regulated process occurs. Excessive fibrin clots are formed in small and mid-size blood vessels, causing thrombotic occlusions and, ultimately, end-organ damage. Coagulation factors are quickly exhausted without adequate physiologic compensation, and bleeding occurs.

Diagnosis

DIC is characterized by prolonged PT/aPTT/TT, thrombocytopenia (typically <100,000/mcL), and microangiopathic hemolytic anemia. The level of fibrinogen may be normal due to pathologic compensation in the early disease stage; however, significant hypofibrinogenemia is found in severe DIC. D-dimer will be markedly elevated and is useful to distinguish DIC from other coagulopathies with thrombocytopenia. The International Society of Thrombosis and Haemostasis developed an algorithm to identify cases of overt DIC. The variables that contribute to the diagnosis of overt DIC include thrombocytopenia (platelet 50,000-100,000/mcL = 1 point, <50,000/mcL = 2 points), elevated D-dimer (moderate elevation = 1 point, severe elevation = 2 points), prolonged PT (prolongation by 3 to <6 seconds = 1 point, ≥6 seconds = 2 points), and

hypofibrinogenemia (<100 mg/dL = 1 point). A score of 5 points or more is consistent with overt DIC.

Management

The primary goal of the management of DIC is to treat the underlying disease causing DIC. However, in most cases, this is not easily or rapidly accomplished, and the patient will need further support. Resuscitation to maintain adequate perfusion is necessary, as acidosis will only exacerbate the coagulopathy. The role of FFP, cryoprecipitate, and platelets is controversial. As with liver disease, FFP can be considered in patients with a prolonged PT greater than 1.5 times the upper normal value. If FFP is not available, or the volume cannot be tolerated, alternate consideration can be given to administration of prothrombin complex concentrate (PCC). While FFP contains all coagulation factors and proteins, PCC contains factors II, VII, IX, and X as well as the anticoagulants proteins C and S. However, given the absence of data, and the potential to increase the thrombotic complications associated with DIC, many experts recommend avoidance of PCC in DIC. In a bleeding patient, platelet transfusions (usually as a single-donor platelet or 4-6 platelet concentrates) are generally given to keep the platelet count above 50,000/mcL. Cryoprecipitate (usually in pools of 10 units) should be considered in the bleeding patient with hypofibrinogenemia to keep the fibrinogen above 60 mg/dL, with some guidance recommending levels greater than 100 mg/dL. The role of antithrombin III concentrates and heparin is controversial in most cases of DIC. Heparin has been useful in cases of subacute DIC associated with acute promyelocytic leukemia, abdominal aortic aneurysm, and purpura fulminans.

UREMIC BLEEDING

Causes

Bleeding in patients with uremia is multifactorial and thought to be secondary to platelet dysfunction, including intrinsic platelet

dysfunction and abnormal platelet-vessel wall interactions. In addition, anemia contributes to increased bleeding because platelets flow more centrally in the vessel, making it less likely that they would interact with the injured vessel wall to initiate hemostasis.

Pathophysiology

Accumulation of toxins (eg, guanidinosuccinic acid) in plasma inhibits normal platelet activation and aggregation. Increased levels of nitric oxide and prostacyclin are found in patients with uremia compared to nonuremic individuals, and these negatively impact platelet adhesion to endothelium and platelet-platelet interactions. Defects in platelet function have been attributed to the environment in which the platelets exist, as incubation of platelets from a patient with uremia patient in normal plasma corrects the dysfunction, whereas placement of platelets from a nonuremic individual in uremic plasma reproduces the defect.

Diagnosis

Patients with uremia usually present with mucosal bleeding, such as gingival bleeding, epistaxis, and hematuria. Less commonly, central nervous system and severe gastrointestinal bleeding may occur. In addition to laboratory changes associated with decreased renal function, patients may present with a decrease in hemoglobin and mild thrombocytopenia, both of which contribute to the bleeding phenotype in uremia. The most common laboratory abnormality, although not routinely performed, is decreased platelet aggregation in response to exogenous agents, demonstrating that this does not alter management. The PT and aPTT are usually normal when uremia is the underlying cause of bleeding.

Management

Hemodialysis or peritoneal dialysis is the most effective method to improve platelet function in patients with uremia and the preferred treatment. Red blood cell transfusions to correct anemia have been shown to decrease bleeding in the acute situation. While the primary

hemostatic defect in uremia is related to platelet dysfunction, platelet transfusion is generally not effective in the patient with bleeding uremia as the transfused platelets rapidly acquire the hemostatic defect of native platelets. Thus, the effectiveness of transfusion is transient. Desmopressin (DDAVP) increases plasma levels of factor VIII, vWF, and tissue plasminogen activator (t-PA) and thus is used by some in the management of bleeding in the patient with uremia, although use is off-label. DDAVP is administered at a dose of 0.3 mcg/kg intravenous (IV) or subcutaneous (SC) every 24 hours with repeated doses carrying a risk of tachyphylaxis. Use of cryoprecipitate in uremic bleeding lacks data and is generally not recommended unless hypofibrinogenemia is concurrently present. Once uremia is corrected (ie, via dialysis or recovery of renal function), the patient's endogenous platelets should be functional.

VITAMIN K DEFICIENCY AND WARFARIN THERAPY

Causes

- Inadequate oral vitamin K intake
- Antibiotics
- Generalized fat malabsorption
- Warfarin therapy
- Rodenticide poisoning (eg. Brodifacoum)

Pathophysiology

Vitamin K is a cofactor for gamma-glutamyl carboxylation, which is required for the function of factors II, VII, IX, and X, protein C, and protein S. Therefore, patients with vitamin K deficiency often present with prolonged PT and elevated international normalized ratio (INR). Major sources of vitamin K are green leafy vegetables, oil, and colonic flora. With a daily intake of 100 to 200 mcg of vitamin K, a healthy adult has 1-week reserve of vitamin K.

Diagnosis

Vitamin K deficiency, or warfarin therapy, results in prolongation of PT and, thus, INR. In cases of severe deficiency or supratherapeutic warfarin therapy, aPTT may also be prolonged. As with liver disease, these prolongations will correct with a 50:50 mix of control plasma. Measuring vitamin K–independent coagulation factors (eg, factor V is decreased in liver disease but not in vitamin K deficiency/warfarin therapy) is useful to distinguish vitamin K deficiency from liver disease. Vitamin K levels are not routinely measured. Ultimately, the diagnosis is made by a shortening of the PT in response to treatment with vitamin K. Failure to correct the PT after vitamin K administration suggests an alternative cause of PT prolongation.

Management

While alternative measures can temporarily correct the underlying factor deficiencies and thus the prolonged PT, vitamin K therapy is the mainstay of therapy for long-term correction. Vitamin K therapy may be given through IV, SC, or enteral routes. In a critically ill bleeding patient, the enteral route should generally be avoided because of high likelihood of gut dysfunction, whereas the SC route should be avoided in patients with perfusion defects or edema. There is a risk of anaphylaxis with IV administration of vitamin K; therefore, this route should be restricted to those situations where the SC or enteral routes are not feasible, and the risk of anaphylaxis is considered justified. Unfortunately, in critically ill patients, this is the most reliable route. We generally administer a single dose of 10 mg orally or parentally, and consider repeating the dose if needed. The effect of vitamin K supplementation should be observed within 24 hours. Adjunctive therapies may be required in the setting of life-threatening bleeding (eg, intracranial bleeding). Considerations for life-threatening bleeding include FFP and PCC. FFP should be given at the initial dose of 10 to 15 mL/kg with concurrent slow administration of 10 mg of IV vitamin K. If 4-factor PCCs (see next paragraph) are available, they may be used instead of FFP for rapid correction.

PCCs are the preferred agents for the reversal of a prolonged INR in the setting of warfarin use. PCCs contain coagulation factors II, IX, and X, with variable amounts of factor VII, protein C, protein S, antithrombin III, and heparin. Dosing is generally based on the patient's weight and INR value, although the use of an alternative strategy of fixed dosing is increasing. The available concentrates are 3- and 4-factor PCC, with 4-PCC containing higher concentrations of factor VII. PCCs are advantageous over FFP in that they offer faster normalization of INR (within 15 minutes), smaller infusion volume, and no need for ABO blood-type matching. Both are relatively safe, with 4-PCC being superior to 3-PCC in correcting INR. As with FFP, use of PCC should be accompanied by vitamin K therapy.

BLEEDING DUE TO DIRECT ORAL ANTICOAGULANTS

Causes

Since 2010, direct oral anticoagulants (DOACs) have emerged as the preferred oral anticoagulants to treat venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), and to prevent thromboembolic events in patients with atrial fibrillation. However, they also require a tailored approach to anticoagulant-related bleeding.

Pathophysiology

The DOACs can be further categorized by their mechanism of anticoagulation, with nomenclature shifting toward this categorization strategy (eg, oral factor Xa inhibitors and oral thrombin inhibitors) as the availability of new classes of anticoagulants is on the horizon (eg, anticoagulants targeting factors XI/XIa and XII/XIIa). The available oral thrombin inhibitor is dabigatran. Dabigatran binds to and inhibits the action of thrombin in cleaving fibrinogen. The factor Xa inhibitors (ie, apixaban, edoxaban, and rivaroxaban) bind to and inhibit the action of factor Xa in cleaving prothrombin. The oral anticoagulants are taken once or twice a day and do not require routine therapeutic drug monitoring, unlike warfarin. Patients are

anticoagulated within a few hours of taking the first dose and will return to their hemostasis baseline within 1 to 2 days of discontinuing the drug (~5 half-lives), assuming adequate renal function.

Diagnosis

A thorough history from the bleeding patient should include recent use of any anticoagulant medication and/or review of the medical record for prescriptions of anticoagulant therapy. While there are currently no United States Food and Drug Administration (FDA)-approved tests to measure DOAC activity, existing tests are sufficiently sensitive to detect the presence of DOACs. A normal TT effectively rules out the presence of sufficient quantities of a direct thrombin inhibitor. A negative anti-factor Xa inhibitor assay, calibrated for heparin or low-molecular-weight heparin, effectively rules out the presence of sufficient quantities of a factor Xa inhibitor. While some labs do have anti-factor Xa inhibitor assays calibrated to apixaban or rivaroxaban, these are not widely available and, thus, are of limited use in most ICUs. While PT and/or aPTT are generally prolonged in the setting of oral anticoagulation, the degree of prolongation does not necessarily correlate with drug concentrations or bleeding risk, and normal values do not always rule out presence. Caution is advised when interpreting PT/INR and aPTT in the setting of oral anticoagulant therapy outside of warfarin.

Management

The mainstay of therapy for control of bleeding in patients on one of the currently available DOACs is cessation of the offending agent. In most patients, the drug will be adequately cleared in approximately 5 half-lives or 1 to 2 days. The half-life of these drugs can be prolonged in the setting of hepatic and especially renal dysfunction. In the setting of life-threatening bleeding, where immediate control is imperative, additional strategies should be employed to control bleeding and reverse therapy.

There are two FDA-approved reversal agents for the DOACs. Idarucizumab was approved by the FDA in 2015 for reversal of

dabigatran based on findings of the RE-VERSE AD trial. It is a monoclonal antibody that binds to dabigatran and neutralizes its activity within minutes. It is given in two 2.5 g boluses that can be sequentially administered. Dabigatran can also potentially be removed by hemodialysis as most of the drug remains unbound in the plasma. Andexanet alfa is a recombinant, modified human factor Xa decoy protein that binds factor Xa inhibitors. It is administered as a bolus followed by infusion, which can take up to 2 hours. With either reversal agent, there are concerns for risk of thrombosis with andexanet alfa having a black box warning given rates of thromboembolism in the trials leading to approval. While no direct comparison is available, case reports and cohort studies suggest similar efficacy between the DOAC reversal agents, idarucizumab and andexanet alfa, and 4-factor PCC. However, thromboembolism remains a concern with 4-factor PCC, and direct trials comparing the safety and efficacy are warranted. Regardless, 4-factor PCC can serve as an option when the direct reversal options are not available.

Common Congenital Disorders of Coagulation

HEMOPHILIA A AND B

Cause

Hemophilia is an X-linked genetic deficiency in a specific coagulation factor that is associated with increased bleeding risk. Most individuals inherit the gene causing the deficiency, but up to 40% of deficiencies are caused by a spontaneous mutation. *Hemophilia A* (factor VIII deficiency)*, the most common type, affects 1 in 5,000 male births and up to 80% of all persons with hemophilia. Hemophilia B* (factor IX deficiency) has an incidence of 1 in 25,000 male births worldwide, which contributes to 20% to 25% of the hemophilia cases. In contrast to factor VIII, which has a half-life of 8 to 12 hours, factor IX has a longer half-life (24-25 hours) and wider tissue distribution. Factor XI deficiency is an autosomal genetic disorder that tends to have a milder course than hemophilia A or B

and is disproportionate to the prolongation of aPTT, and will not be discussed here.

Pathophysiology

In general, factor VIII and factor IX levels of 30% or more are sufficient for normal coagulation. With decreasing amounts of these factors, *in vivo* hemostasis is impaired. Primary hemostasis and platelet function are normal.

Diagnosis

Patients with severe hemophilia may experience spontaneous bleeding, especially of the joints, soft tissue, and genitourinary tracts. However, patients with mild hemophilia may only bleed after surgical intervention or trauma and occasionally with no bleeding history. Individuals with hemophilia will have an isolated prolongation of the aPTT. The final diagnosis is made by measuring factor VIII and IX levels, with results showing decreased factor VIII or IX levels in the patient's plasma. *The severity of hemophilia is categorized into mild, moderate, and severe forms correlating with the degree of factor VIII deficiency (6%-30%, 2%-5%, and <1%, respectively). Of note, in mothers of patients with hemophilia lyonization—or the mosaic inactivation of unaffected X chromosome—may lead to low factor levels and potentially a bleeding diathesis that is not fully appreciated. The bleeding of hemophilia carriers with low factor levels is specifically appreciated during menses and the perinatal period.*

Management

Treatment depends on the severity of the hemophilia and the severity of bleeding.

Hemophilia A: DDAVP may be used to increase factor VIII activity by 3- to 5-fold in patients with mild and moderate forms of hemophilia A and minor bleeding. The typical dose, given IV, is 0.3 mcg/kg. The expected rise in factor VIII should occur within 5 to 8 hours. Not all patients with hemophilia will respond to DDAVP; thus,

a prior history of response is helpful. Finally, to decrease the possibility of tachyphylaxis, no more than three doses should be given. Patients with severe hemophilia and any bleeding or those with mild to moderate hemophilia and severe bleeding will require factor VIII replacement. Factor VIII is replaced with either viral-inactivated plasma-derived or recombinant products. Both are effective, and an individual choice is usually made on the basis of availability. Factor VIII is dosed by the patient's weight. A unit of factor VIII concentrate should increase the plasma activity of factor VIII by 2% per kg of body weight. The goal of replacement therapy in patients with minor bleeding is a factor VIII activity of 25% to 30%; with moderate-to-severe bleeding, it is 50%; and with surgical or life-threatening bleeding, it is 75% to 100%. Factor VIII concentrate has a half-life of 8 hours, and activities should be monitored during treatment. Dosing is usually repeated every 8 to 12 hours, depending on the measured plasma activities of factor VIII. An alternative option is a continuous infusion of factor VIII; however, we recommend a hematology consult for this approach. Treatment should be continued until the bleeding is stabilized. In the surgical patient, factor replacement is typically continued for up to 10 to 12 days after the procedure, with duration varying based on the type of surgery and prior response to replacement if known.

Some patients with hemophilia A will develop inhibitors to factor VIII replacement therapy, thus rendering factor VIII replacement ineffective. In the presence of a low titer inhibitor (ie, Bethesda units [BU] <5), factor VIII concentrate at high doses may still be effective. However, most patients with inhibitors will require treatment with recombinant activated factor VII (rFVIIa). rFVIIa is given at a dose of 90 to 120 mcg/kg every 2 hours and should be continued until hemostasis is achieved. In patients with an inhibitor who cannot achieve hemostasis with a bypassing agent, recombinant porcine factor VIII (Obizur) can be used to acquire hemostasis. However, cross-reacting antibodies can occur, and alloantibodies limit the duration of therapy with nonhuman forms of factor VIII. Regardless of the agent, these patients may consume enormous amounts of

factor concentrates and should be managed by an experienced hematologist.

Emicizumab, a bispecific humanized monoclonal antibody approved as prophylaxis for patients with hemophilia A with or without inhibitors, works by bridging activated factors IX and X, thereby replacing the need for factor VIII. Given the drug mechanism, routine measurement of factor VIII activity in these patients will be falsely elevated, and a chromogenic assay with bovine factor IX is required to assess the circulating factor levels. Emicizumab is typically insufficient for the treatment of hospitalized patients with hemophilia and bleeding. Further, assays of "global coagulation" (TEG and thrombin generation) are not applicable for assessing treatment response. In addition, aPTT-based factor VIII activity assays cannot be followed in these patients for dosing. Consultation with an experienced hematologist is recommended.

***Hemophilia B*:** Plasma-derived and recombinant factor IX products are available for replacement therapy. Unlike in hemophilia A, DDAVP is ineffective in all patients with hemophilia B. Each unit of factor IX concentrate should raise the plasma factor IX activity by 1% per kg of body weight. Factor IX's half-life is 24 hours, and therefore dosing should occur at 18- to 24-hour intervals. The subsequent doses are usually half the initial dose, but monitoring of plasma activities will help to adjust the dose as necessary. The target plasma activities of factor IX are similar to those noted earlier for factor VIII. Bleeding patients with inhibitors to factor IX should be treated with rFVIIa, as noted earlier for patients with inhibitors to factor VIII, and should be guided by an experienced hematologist. Newer extended half-life technologies have decreased the amount of product infusion requirements and may be reviewed in supplemental readings below.

***Acquired Hemophilia*:** Patients without a bleeding history may exhibit low levels of factor through a bleeding diathesis, with an isolated prolonged aPTT that does not correct with 50% factor levels (as occurs in a mixing study). Typically, bleeding occurs in soft tissue spaces (as compared to congenital hemophilia). In such an event, autologous antibodies are formed against endogenous factors.

These antibodies are functionally measured as in patients with congenital hemophilia (BU) and treated similarly as patients with hemophilia with inhibitors with the notable addition of immunosuppression (including high-dose steroids, rituximab, or cyclophosphamide) to eradicate the inhibitory antibody under the direction of an experienced hematologist.

VON WILLEBRAND DISEASE

Causes

vWD is a genetic disease caused by a deficiency or qualitative defect in vWF. It is the most common inherited bleeding disorder and is most often inherited in an autosomal dominant manner; therefore, men and women are equally affected.

Pathophysiology

vWF is a carrier molecule for factor VIII, and normal levels are needed to maintain adequate levels of factor VIII in circulation. In addition, vWF is necessary for platelet adhesion to the vessel wall at sites of injury and, thus, is essential for normal platelet function (primary hemostasis). There are several types of vWD, ranging from mild to severe quantitative disorders, and several types with qualitative defects.

Diagnosis

Patients with vWD present predominately with mucocutaneous bleeding (eg, bleeding from gums and menorrhagia in women) and easy bruising. vWF antigen, vWF activity (preferably assayed by its ability to bind its platelet receptor GP1b or ristocetin cofactor [RCo] activity), and factor VIII activity are measured to determine the type of vWD. Types I (mild) and III (severe) are quantitative defects of vWF, whereas type II (subdivided into several different defects) is a qualitative defect. von Willebrand multimer studies may be necessary to determine the type of vWD that is critical to bleeding management and medical interventions.

Management

DDAVP, which promotes the release of vWF, has been shown to be beneficial in raising the vWF in type 1 and certain patients with type 2 vWD. It should not be used in individuals diagnosed with type IIB vWD or type III. vWD type IIB is characterized by increased vWF-binding platelets at a steady state, which leads to the clearance of both. Therefore, when DDAVP increases the release of this dysfunctional vWF, it will lead to decreased platelet counts and has the potential to increase bleeding. Conversely, patients with type III have no vWF stores to stimulate increased circulating vWF. If individuals are refractory to DDAVP or are severely deficient in vWF (type III vWD), vWF/FVIII concentrate should be given. The initial dose in severe bleeding or surgery is 40 to 60 RCo units/kg, followed by 20 to 40 RCo units/kg every 12 to 24 hours to keep vWF activities at 50% to 100% for 7 to 14 days. For milder bleeding and surgery, an initial dose of 30 to 60 RCo units/kg should be given, followed by 20 to 40 RCo units/kg every 12 to 48 hours to keep the vWF above 30% for 3 to 5 days. There are two common products to replace vWF: either recombinant vWF (ie, Vonvendi) or plasma-derived vWF (ie, Humate-P). Care should be taken in replacement with plasma-derived vWF products as they will also contain factor VIII and will be labeled with dosing for each—which are not interchangeable. Antifibrinolytic agents (eg, aminocaproic acid and tranexamic acid) may be helpful adjuvant treatments to achieve hemostasis in patients bleeding from mucosal surfaces.

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67 Transfusion Practices

Vladimir N. Despotovic and Jason Y. Ross

Anemia is a common problem in the intensive care unit (ICU) setting. In critically ill patients, oxygen delivery and oxygen consumption may be impaired by factors such as decreased cardiac output, decreased red-cell mass, decreased circulating blood volume from red blood cell (RBC) loss, and altered acid-base status. Causes of anemia in this setting are varied and include overt blood loss from bleeding, frequent blood draws, hemolysis, a functional decrease in usable iron, and decreased erythropoietin production.

Anemia is traditionally treated with infusions of RBCs to increase oxygen-carrying capacity and tissue delivery of oxygen. Various studies have estimated that more than 40% of all ICU patients receive blood transfusions and that more than two-thirds of these transfusions were not for acute blood loss.

In most critically ill patients, the transfusion trigger of hemoglobin (Hb) less than 7 g/dL is recommended. The Transfusion Requirements in Critical Care (TRICC) was the original randomized control trial (RCT) that compared a restrictive (Hb <7 g/dL) versus liberal (Hb <10 g/dL) transfusion threshold in critically ill patients. Compared to liberal transfusion, there was a trend toward decreased mortality in the restrictive arm. Thirty-day mortality rates were lower with a restrictive strategy in less severely ill patients (APACHE II score ≤20) and patients less than 55 years of age. Furthermore, rates of myocardial infarction and pulmonary edema were lower in the restrictive group.

The transfusion thresholds in septic shock (TRISS) trial showed that in septic shock, a restrictive transfusion strategy (Hb ≥7 g/dL) compared to a liberal transfusion strategy (Hb ≥9 g/dL) had similar mortality at 90 days with 50% fewer units of blood transfused in the restrictive group.

Among hemodynamically stable patients with an acute upper gastrointestinal (GI) bleed, a restrictive transfusion strategy appears to be safe. One single-center RCT assigned 921 patients with acute upper GI bleed to a restrictive transfusion strategy (Hb <7 g/dL) or liberal transfusion strategy (Hb <9 g/dL). The restrictive arm had a higher probability of survival at 6 weeks as well as fewer overall complications and less subsequent bleeding. Notably, massive GI bleeds and patients who are hemodynamically unstable were excluded from the trial, and 51% of the patients in the restrictive transfusion trigger group never received any blood. Similarly, a multicenter trial of 936 patients with acute upper GI bleed found no significant difference in clinical outcomes between a restrictive (Hb <8 g/dL) versus a liberal (Hb <10 g/dL) transfusion strategy. In the setting of a massive bleed, the transfusion practices and blood product ratios should be guided by the clinical situation and the clinician's experience.

Under the circumstances of coronary artery disease (CAD) and acute coronary syndromes (ACSs), more trials are needed to clarify the beneficial transfusion goals. In the recent restrictive and liberal transfusion strategies in patients with Acute myocardial infarction (REALITY) trial, 668 patients with ACS were randomized to a restrictive (Hb ≤8) or liberal (Hb ≤10) transfusion strategy. A trend toward lower risk of major adverse cardiac events (MACE) at 30 days was seen in the restrictive group. In addition, adverse events were similar between the two groups. Interestingly, among survivors who were followed for 1 year, major cardiac events appeared to be more frequent in the restrictive group. A smaller pilot trial looking at patients with ACS undergoing cardiac catheterization found death at 30 days to be less frequent in the liberal transfusion goal group for Hb less than 10 g/dL as compared to the more restrictive goal for Hb less than 8 g/dL. Nevertheless, transfusion practices must take into account systemic organ dysfunction that may affect oxygen delivery, anticipated blood losses, and overall patient morbidity, resulting in patient- and situation-specific use of RBCs and other blood products. The large ongoing Myocardial Ischemia and Transfusion (MINT) trial

should provide guidance on safe transfusion thresholds in the setting of ACS.

Among patients with stable preexisting CAD, high-quality evidence in support of a liberal versus restrictive transfusion strategy is lacking. However, results taken from randomized trials that have included patients with CAD reveal that cardiac events are similar between restrictive versus liberal transfusion groups. Thus, a Hb transfusion threshold of 7 to 8 g/dL appears to be reasonable. Likewise, in patients with congestive heart failure, there are no large RCTs to guide practice. Transfusion should be considered when Hb is less than 7 to 8 g/dL. Among patients undergoing cardiac surgery with cardiopulmonary bypass, a 2021 meta-analysis of several trials (including the large transfusion requirements in critical care [TRICC] III trial) supports a Hb transfusion threshold of 7.5 to 8 g/dL.

In massive transfusions, various protocols have been institutionally developed, and the data come from patients with severe trauma. The initial transfusions are based on the degree of bleeding and the hemodynamic instability. Serial monitoring of Hb level, platelets, prothrombin time/international normalized ratio (Pt/Inr), partial thromboplastin time (Ptt), fibrinogen, and, if available, viscoelastic testing should be performed. In the initial resuscitation in a severe trauma setting, fresh frozen plasma (FFP):platelets (Plt):RBC ratio of 1:1:1 appears to be well supported. In the nontraumatic setting, there is insufficient data available, and different ratios ranging from 1:1:1 to 2:1:4 are used. Following and correcting the acid-base status, hypocalcemia and hypothermia should be a part of the protocol. Antifibrinolytic therapies, factor concentrates, and recombinant factor VII use should also be considered.

In patient populations who refuse blood transfusions on a cultural, religious, or personal belief basis, their wishes should be honored. The most well-known religious group that commonly declines blood transfusions is Jehovah’s Witnesses. Confirmation of the patient’s understanding of short- and long-term risks and the benefits should be obtained. For a patient who is bleeding, anemic in the ICU setting, aggressively controlling the bleeding source, minimizing phlebotomy, stress ulcer prophylaxis, administration of

erythropoiesis-stimulating agents and IV iron to maintain ferritin greater than 100 ng/mL, and transferrin saturation more than 20% are most commonly used. Empiric folate and vitamin B_{12} to support hematopoiesis is also reasonable. Careful review of medications should be performed, and if possible, medications that could increase bleeding should be discontinued, and antifibrinolytic or, if acceptable, recombinant factor therapy should be considered.

Dosing and Administration

Each unit of packed RBCs is approximately 300 mL and is generally given during 2 to 3 hours. One unit of packed RBCs is expected to increase Hb by approximately 1 g/dL and raise the hematocrit by approximately 3% in a healthy individual without ongoing blood loss or destruction. Before transfusions, the patient's blood should be tested for ABO status, but type O-negative RBCs can be given in emergency situations.

Types of Red Blood Cell Products

Table 67.1 presents some of the various blood products and their indications. Included in this section is further discussion of common products.

TABLE 67.1 Blood Products

Product	Indications	Comments

Product	Indications	Comments
Packed red blood cells	• Increase oxygen-carrying capacity in patients with anemia. • Can be used to increase blood volume in acute loss	• Transfusions to keep Hgb ≥7 g/dL in ICU setting • Data support higher levels in ACS (Hb >8 g/dL).
Platelets	• Thrombocytopenia with high risk of bleeding • *Not* indicated in the presence of increased destruction without bleeding	• Prophylactic transfusion only if platelet count <10,000/mcL • Maintain platelet count ≥50,000/mcL with active bleeding or in anticipation of an invasive procedure. • Thresholds for procedures vary by institution.
Fresh frozen plasma	• Bleeding in setting of factor deficiency or coagulopathy • Warfarin reversal • Severe DIC	• Dosage ranges from 5 to 15 mL/kg, but generally start with 2 units and recheck PT/PTT.
Cryoprecipitate	• Fibrinogen deficiency	• Contains fibrinogen as well as vWF, factors VIII, XIII, and fibronectin
Humate-P	• vWD types 2B, 2N, 3	• A specific vWF-containing factor VIII concentrate
Factors VIII and IX concentrate	• Hemophilia A and B treatment, respectively	• Virally inactivated • Recombinant technologies have eliminated infectious risks.

Product	Indications	Comments
Recombinant factor VIIa 4-factor prothrombin complex concentrate	• Bleeding complications in acquired hemophilia A and B • Factor VII deficiency • Used in life-threatening bleeds in the setting of vitamin K antagonists or direct factor Xa inhibitors	• Recombinant • Used for surgery and acute bleeding in hemophilia • Contains factors II, VII, IX, and X

ACS, acute coronary syndrome; DIC, disseminated intravascular coagulation; Hgb, hemoglobin; ICU, intensive care unit; PT/PTT, prothrombin time/partial thromboplastin time; vWD, von Willebrand disease; vWF, von Willebrand factor.

WHOLE BLOOD

Whole blood is currently used in autologous donation situations (before surgery and so forth). Whole blood contains all normal constituents of human plasma, including RBCs, platelets, and plasma proteins.

PACKED RED BLOOD CELLS

Packed RBCs contain approximately 200 mL of RBCs resuspended in a preservative solution. Each bag has a hematocrit of approximately 55% to 60% and approximately 200 to 250 mg of iron.

LEUKOREDUCED RED BLOOD CELLS

Leukocytes are filtered out to decrease human leukocyte antigen (HLA) sensitization in patients who are chronically transfused (ie, hematologic malignancies) as well as in potential kidney, heart, and lung transplant candidates. In addition, leukoreduced blood and cytomegalovirus (CMV) antibody-negative blood are used in patients who are known to be CMV-negative and are at high risk for complications if infected with CMV (eg, transplant patients and pregnant patients). Leukoreduced blood can also be used to

decrease the risk of febrile nonhemolytic transfusion reactions (FNHTR).

GAMMA-IRRADIATED RED BLOOD CELLS

External beam radiation is applied to the unit of blood to produce gamma-irradiated blood. This allows for the destruction of donor T lymphocytes for the prevention of transfusion-associated graft-versus-host disease (TA-GVHD) in stem cell transplant patients and severely immunocompromised patients.

SALINE-WASHED RED BLOOD CELLS

The donor cells are processed with normal saline to remove as much of the donor serum as possible. This is most commonly used in patients who are immunoglobulin A (IgA)-deficient and at high risk for anaphylaxis during transfusions, as well as in patients with paroxysmal nocturnal hemoglobinuria to deplete complement.

Risk of Transfusions

Transfusion of blood products carries risks. These risks can be divided on the basis of whether the complication is short term (related to each unit that is transfused) or long term (proportional to the total number of units that a patient receives over their lifetime).

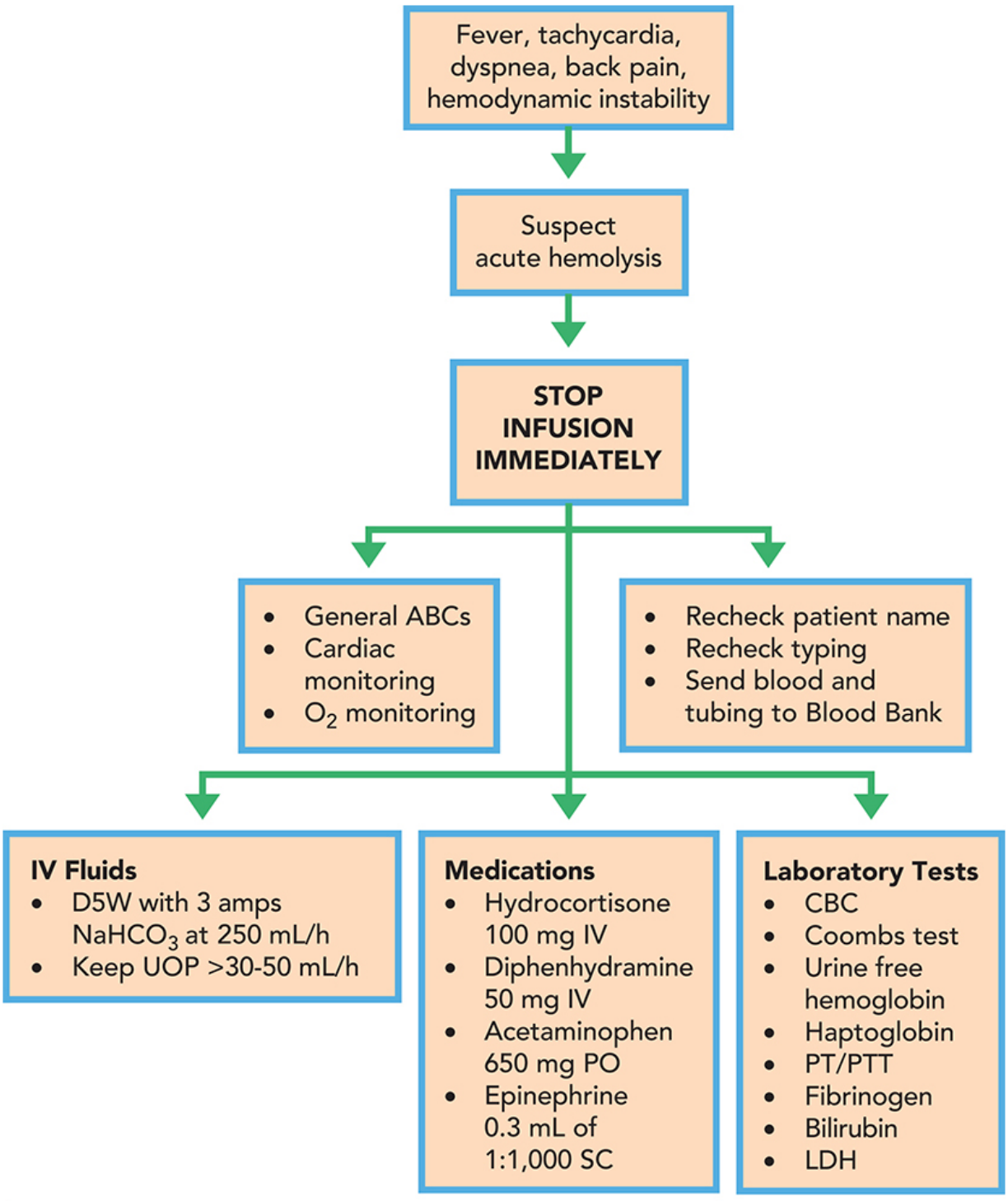
ACUTE TRANSFUSION RISKS

Acute Hemolytic Reactions

The most serious and immediately life-threatening complication of transfusions is an acute hemolytic reaction. This is due to preformed antibodies (usually IgM) in the recipient's serum against major antigens present on the donor RBCs (most commonly A, B, or Kidd antigens) and results in acute intravascular hemolysis. These reactions occur with an estimated frequency of 1 in 250,000 to 1 in

1,000,000 and initially manifest acutely as fever, dyspnea, tachycardia, back pain, hypotension, chills, and chest pain within the first several minutes of the transfusion. Workup is notable for hemoglobinemia, hemoglobinuria, positive direct antigen testing, elevated bilirubin and lactate dehydrogenase (LDH), undetectable haptoglobin, and spherocytes on a peripheral blood smear. If an acute hemolytic reaction is suspected, *the infusion should be stopped immediately*, and the blood bank notified. Algorithm 67.1 outlines management strategies for acute hemolytic reactions.

ALGORITHM 67.1 **Management of Acute Hemolytic Reaction**


Fever, tachycardia, dyspnea, back pain, hemodynamic instability
Suspect acute hemolysis
STOP INFUSION IMMEDIATELY
General ABCs
Cardiac monitoring
O_2 monitoring
Recheck patient name
Recheck typing
Send blood and tubing to Blood Bank
IV Fluids
D5W with 3 amps $NaHCO_3$ at 250 mL/h
Keep UOP >30-50 mL/h
Medications
Hydrocortisone 100 mg IV
Diphenhydramine 50 mg IV
Acetaminophen 650 mg PO
Epinephrine 0.3 mL of 1:1,000 SC
Laboratory Tests
CBC
Coombs test
Urine free hemoglobin
Haptoglobin
PT/PTT
Fibrinogen
Bilirubin
LDH
ABBREVIATIONS
IV: intravenous
D5W: 5% dextrose in water
UOP: PO, orally
SC: subcutaneously
CBC: complete blood count

PT/PTT: prothrombin time/partial thromboplastin time
LDH: lactate dehydrogenase
ABC: airway, breathing, and circulation

Nonhemolytic Febrile Reactions

Nonhemolytic febrile reactions occur in approximately 1% of transfusions and are the result of antibodies in the recipient's serum against white blood cells in the donor's product. This manifests acutely, usually within 1 to 6 hours, as an increase in body temperature and is more common in patients who have been previously alloimmunized by numerous transfusions. Workup for hemolysis is negative. This reaction is treated with antipyretic medications and can be avoided by transfusing leukoreduced blood products.

Allergic Reactions

Allergic reactions occur as a result of recipient IgE-mediated hypersensitivity to donor plasma proteins. They occur in approximately 1 in 100 transfusions and typically manifest as localized or diffuse urticaria as well as bronchospasms. This condition is treated with antihistamine medications and can be avoided by transfusing washed blood products. However, a potentially severe form may be encountered in IgA-deficient individuals who can have anaphylactic reactions to serum from non–IgA-deficient donors. This is best prevented with washed RBCs but can be treated with intramuscular epinephrine, high-dose corticosteroids, airway protection, and antihistamines.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) occurs by an incompletely understood mechanism, but an immune antibody-mediated process has been established in a majority of cases. A nonimmune mechanism has been postulated as well. Data from animal models and clinical studies suggest that both processes occur and that TRALI may be the end result of diffuse neutrophil

activation and capillary leak by these mechanisms. TRALI occurs within 1 to 6 hours of transfusion, resulting in diffuse capillary damage in the pulmonary vasculature. It presents as rapid-onset dyspnea, hypoxia, fever, and bilateral pulmonary infiltrates resembling acute respiratory distress syndrome in the absence of volume overload or heart failure. Treatment is supportive as most cases are self-limiting, but patients may require mechanical ventilation.

Bacterial Infection

Blood units, most commonly platelets, can be contaminated with bacterial agents, including cold-growing organisms such as *Yersinia enterocolitica*, as well as various gram-negative organisms. Transfusion of infected blood products can manifest as a septic-like picture with high fevers, rigors, and hypotension. If suspected, Gram stain and blood cultures should be obtained from both the recipient and blood product bag, and antibiotics should be promptly initiated. With chronic infections like syphilis, routine testing for *Treponema pallidum* is performed. Incidence of bacterial infection has dramatically decreased since the introduction of disposable plastic blood bags.

LONG-TERM TRANSFUSION RISKS

Delayed Hemolytic Reactions

Delayed hemolytic reactions usually occur more than 24 to 48 hours (and up to 7-10 days) after a transfusion. Delayed reactions result from antibodies in the recipient's serum that are directed toward minor antigens on the donor's RBCs (typically Kidd, Duffy, or Kell antigens), which are produced by an anamnestic response. This usually manifests as an asymptomatic but sudden decrease in Hb concentration, mild flu-like symptoms, and laboratory evidence of hemolysis, including a positive direct Coombs test and increased indirect bilirubin concentration.

Viral Infections

Infectious complications of blood transfusions are located in Table 67.2. All blood products are currently screened for hepatitis B, hepatitis C, human immunodeficiency virus 1 and 2, and human T-lymphotropic virus I and II. In the United States, West Nile virus and Zika virus testing have been added to the screening process. Other infectious risks include viruses that are not universally screened for, such as CMV and parvovirus B19, and the prion-transmitted Creutzfeldt-Jacob disease.

TABLE 67.2 Transfusion-Associated Infections

Virus	Risk Factor (per million)	Estimated Frequency (per unit)	No. of Deaths (per million units)
Hepatitis A	1	1/1,000,000	0
Hepatitis B	7-32	1/30,000-1/250,000	0-0.14
Hepatitis C	4-36	1/30,000-1/150,000	0.5-17
HIV	0.4-5	1/200,000-1/2,000,000	0.5-5
HTLV I and II	0.5-4	1/250,000-1/2,000,000	0
Parvovirus B19	100	1/10,000	0

HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

Data from Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine. First of two parts—blood transfusion. *N Engl J Med*. 1999;6:438-441.

Other Infections

Chronic protozoan infections like Chagas disease and babesiosis can occasionally be transmitted through transfusion and are minimized through selective screening processes.

Iron Overload

Although not typically an issue in the ICU setting, secondary iron overload syndromes occur in proportion to the number of blood products a patient receives. Patients at highest risk include those with multiple transfusions over long periods of time (eg, sickle-cell disease, thalassemia, and myelodysplastic syndrome). Each milliliter of packed RBCs contains approximately 1 mg of iron. Patients who are repeatedly transfused in the absence of blood loss are at risk of overwhelming the body's ability to use iron with resultant deposition into tissues such as the myocardium, bone marrow, and liver.

Posttransfusion Purpura

In posttransfusion purpura (PTP), human platelet antigen (HPA)-1A-negative recipients develop antibodies to HPA-1A antigens commonly found on donor platelets. This results in platelet destruction, thrombocytopenia, and purpura with mucocutaneous bleeding. PTP is rare and typically occurs in women 3 to 14 days after platelet transfusion. Diagnosis is confirmed with the detection of anti-HPA-1A antibody and can be treated with intravenous immunoglobulin (IVIG) or plasmapheresis.

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A prospective observational study of patients in European ICUs evaluating the prevalence of anemia and transfusion use in this setting.

68 Hypercoagulable States

Marin H. Kollef, Vladimir N. Despotovic, and Morey A. Blinder

Hypercoagulable states are a heterogeneous group of inherited or acquired disorders that predispose individuals to inappropriate clot formation in the venous or arterial circulation. The inappropriate formation of thrombi typically occurs in the presence of Virchow triad of hypercoagulability, stasis, and endothelial damage. Embolization of these clots can occur, resulting in pulmonary embolism (PE) in the case of venous embolic disease, or emboli to vital organs in the setting of arterial thrombosis.

Various manifestations of hypercoagulability are demonstrated in the intensive care unit (ICU) setting. Patients are at an increased risk of venous thromboembolic disease because of their prolonged immobilization, procedures, and intravascular devices that they are exposed to; bacteremia or other infections; and their underlying disease states. Patients in the ICU setting may have transient risk factors for thromboembolic disease, or may in addition have underlying predisposing genetic or acquired conditions such as cancer that increase their risk. Notably, previous thromboembolic events are a prominent risk factor for future thromboembolism, particularly if they occurred without surgical or clear precipitating factors. Listed in Table 68.1 are common causes of hypercoagulability.

TABLE 68.1 Causes of Hypercoagulability

Acquired Causes	Inherited Causes
Trauma/surgery	Factor V Leiden mutation

Acquired Causes	Inherited Causes
Malignancy	Prothrombin G20210A mutation
Immobilization	Protein C deficiency
Nephrotic syndrome	Protein S deficiency
Obesity	Antithrombin deficiency
Pregnancy	Increased factor VIII activity
Oral contraceptive use	Dysfibrinogenemia
Congestive heart failure	
Myeloproliferative disorders	
Antiphospholipid antibodies	
Lupus anticoagulant	
Anticardiolipin antibodies	
Heparin-induced thrombocytopenia (HIT)	
Paroxysmal nocturnal hemoglobinuria (PNH)	
COVID-19	
Inflammatory bowel disease	
Sepsis with or without disseminated intravascular coagulation	

An important condition associated with a hypercoagulable state is coronavirus disease 2019 (COVID-19). In addition to all the elements of Virchow triad, COVID-19 results in hypercoagulability via

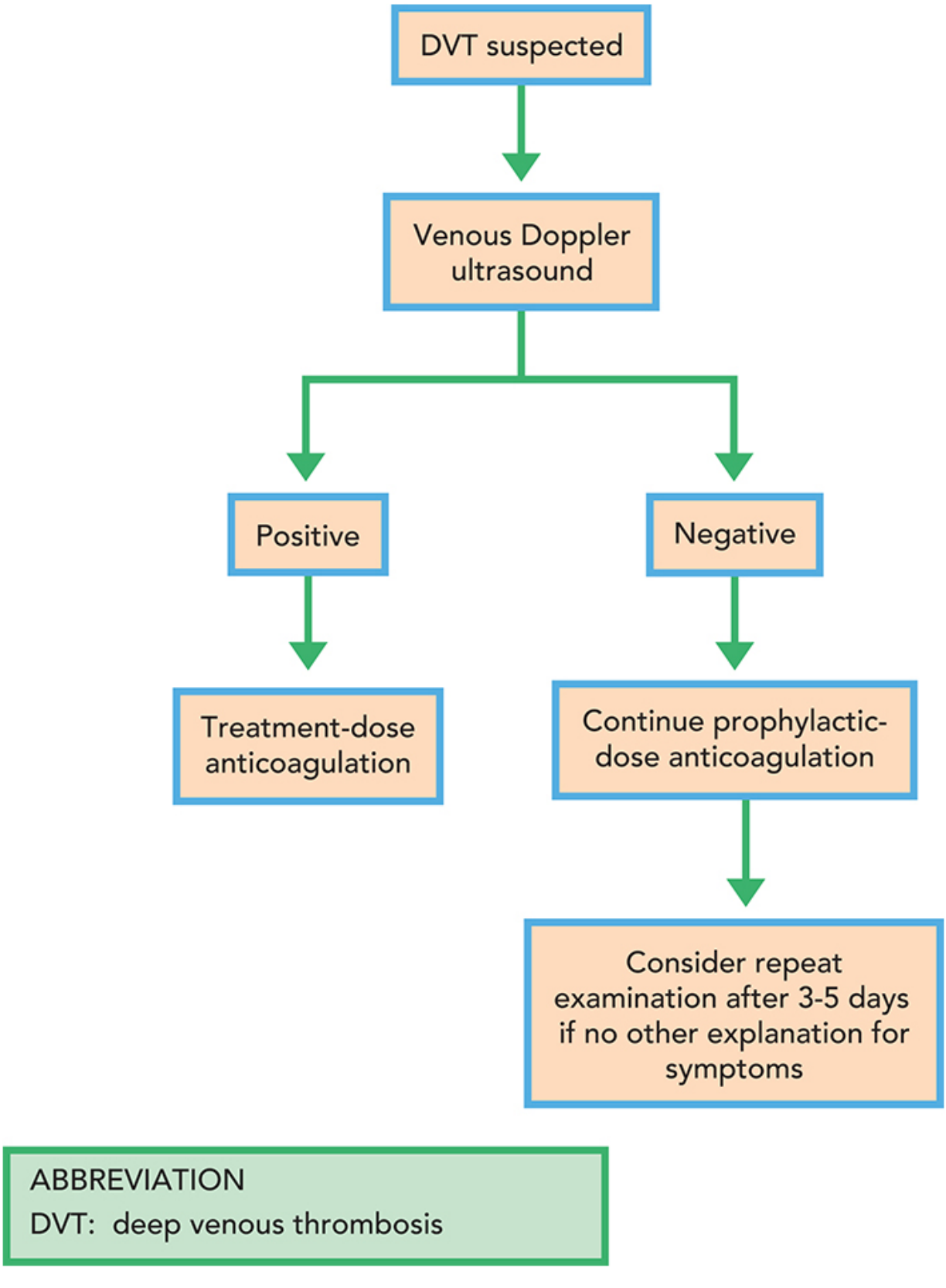
thromboinflammation or COVID-19–associated coagulopathy (CAC). CAC is thought to be different than disseminated intravascular dissemination and is suggested by the presence of elevated fibrinogen, D-dimer, and circulating cytokines in the presence of COVID-19 infection.

Deep Venous Thrombosis and Pulmonary Embolism

Deep venous thrombosis (DVT) and PE are very common in the ICU and are likely underdiagnosed. Some observational studies have demonstrated a 20% to 40% incidence of DVT in the ICU setting depending on patient population and disease acuity.

Diagnosis of DVT and PE in the ICU can be challenging (Algorithms 68.1 and 68.2). Various studies have demonstrated that 10% to 100% of DVTs diagnosed by ultrasound in this setting were not found on physical examination. Furthermore, patients in the ICU setting have a number of factors confounding the diagnosis, including their numerous comorbid conditions, inability to communicate symptoms, numerous procedures and medications, and inability to undergo various diagnostic tests. Table 68.2 lists the diagnostic modalities for DVT and PE commonly employed in the ICU.

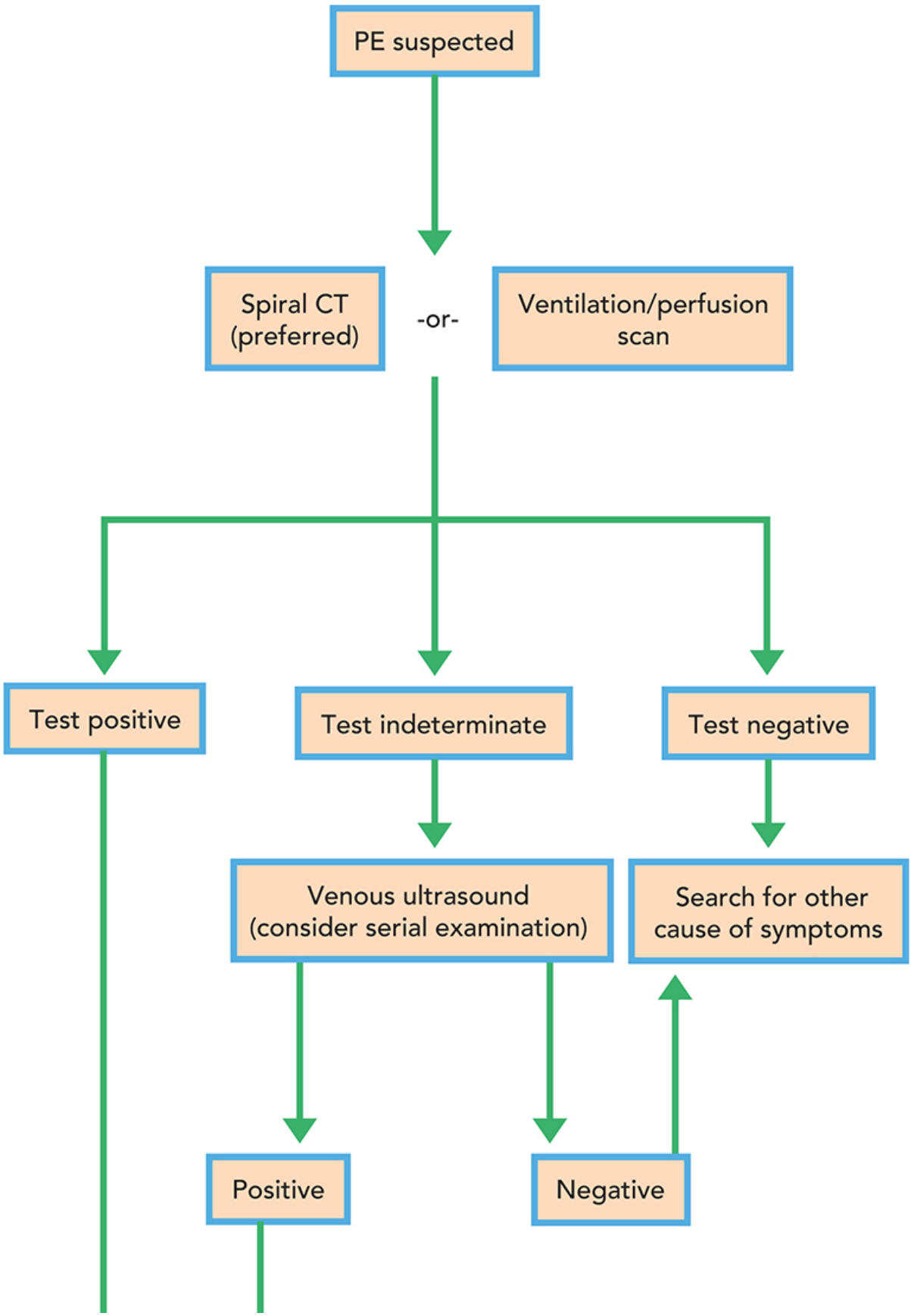
ALGORITHM 68.1 **Algorithm for Diagnosis of DVT**

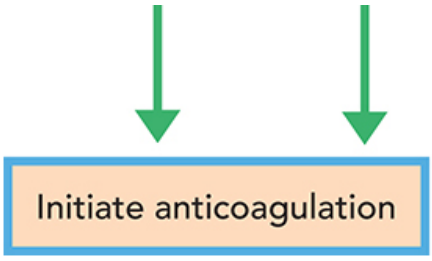


ABBREVIATION

DVT: deep venous thrombosis

ALGORITHM 68.2 Algorithm for Diagnosis of PE


PE suspected
Spiral CT (preferred)
-or-
Ventilation/perfusion scan
Test positive
Test indeterminate
Test negative
Venous ultrasound (consider serial examination)
Search for other cause of symptoms
Positive
Negative



ABBREVIATIONS
CT: computed tomography
PE: pulmonary embolism

TABLE 68.2 Diagnostic Tests for Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) in the Intensive Care Unit Setting

Test	Indication for Testing	Key Points
Venous duplex ultrasound	Suspected DVT in extremities	• Good sensitivity and specificity for proximal DVT
Spiral computed tomography	Suspected PE	• Good sensitivity for large PEs • Contrast bolus predisposes to nephrotoxicity
Ventilation perfusion scanning	Suspected PE	• Good sensitivity for PEs • Difficult to interpret in the setting of recent pneumonia or other infiltrative processes
Computed tomography angiography/venography	Suspected DVT or PE	• Not widely available • Large bolus of contrast used

Adapted from Cook D, Douketis J, Crowther MA, et al. The diagnosis of deep venous thrombosis and pulmonary embolism in medical-surgical intensive care unit patients. *J Crit Care*. 2005;25:314-319, with permission.

Treatment of DVT and PE should commence when clinically suspected if no contraindications exist. As previously mentioned, diagnosis can be difficult in the ICU setting, but delay in treatment can lead to increased morbidity and mortality. Clinically suspected

DVT or PE should be treated with weight-based unfractionated heparin or in a more stable patient with low-molecular-weight heparin. Our preference in critically ill patients is unfractionated heparin or in the setting of suspected heparin-induced thrombocytopenia (HIT), bivalirudin or argatroban, since both agents are shorter acting, can be stopped for bleeding or procedures, and can be adjusted for renal dysfunction. In addition to the oral vitamin K antagonist, warfarin, multiple new direct oral anticoagulants (DOACs) that function as direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have been introduced. Due to their long half-life and kidney-dependent pharmacokinetics, these agents should have limited use in the ICU setting. Dosing guidelines for unfractionated heparin and some alternatives are listed in Tables 68.3 and 68.4.

TABLE 68.3 Weight-Based Unfractionated Heparin Dosing

Initial Dose	
Bolus 80 U/kg	
Infusion 18 U/kg/h	
Adjustment: **aPTT**[a]	
<40	IV 25 U/kg bolus and increase infusion by 2 U/kg/h
40-44	Increase infusion rate by 1 U/kg/h
45-70	No change
71-80	Decrease infusion by 1 U/kg/h
81-90	Hold infusion for 30 min, decrease infusion rate by 2 U/kg/h
>90	Hold infusion for 1 h, decrease infusion rate by 3 U/kg/h

aPTT, activated partial thromboplastin time; IV, intravenous.
[a]aPTT should be drawn 6 h after any adjustment to dose. This is just one example of a nomogram using weight-based heparin dosing. Each institution should establish a heparin weight-based nomogram for unfractionated heparin administration according to the assay employed.

TABLE 68.4 Alternative Anticoagulants

Drug	Mechanism of Action	Use	Prophylaxis Dosing	Therapeutic Dosing
Enoxaparin	Inactivation of factor Xa	Prophylaxis and treatment of DVT/PE	40 mg SC q24h	1 mg/kg SC q12h or 1.5 mg/kg SC q24h
Dalteparin	Inactivation of factor Xa	Prophylaxis and treatment of DVT/PE	5,000 units SC q24h	100 U/kg SC q12h or 200 U/kg SC q24h
Fondaparinux	Inactivation of factor Xa	Prophylaxis and treatment of DVT/PE, HIT	2.5 mg SC q24h	5 mg SC q24h if <50 kg or 7.5 mg SC q24h if 50-100 kg or 10 mg SC q24h if .100 kg
Argatroban	Direct thrombin inhibitor	Treatment of thrombosis in HIT	None	2 mcg/kg/min IV or 0.5-1.2 mcg/kg/min if total bilirubin .1.5 mg/dL

Drug	Mechanism of Action	Use	Prophylaxis Dosing	Therapeutic Dosing
Bivalirudin	Direct thrombin inhibitor	Treatment of thrombosis most commonly in the setting of HIT	None	Adjusted by CrCl 0.15 mg/kg/h (see reference below)
Rivaroxaban	Factor Xa inhibitor	Prophylaxis and treatment of DVT/PE	10 mg po q24h	15 mg po q12h for 3 wk, then 20 mg q24h
Apixaban	Factor Xa inhibitor	Prophylaxis and treatment of DVT/PE	2.5 mg PO q12h	10 mg PO q12h for 1 wk, then 5 mg q12h
Dabigatran	Direct thrombin inhibitor	Prophylaxis and treatment of DVT/PE	110 mg first day, then 220 mg q24h	Parenteral anticoagulation for 5-10 d, then dabigatran 150 mg q12h

CrCl, creatinine clearance; DVT, deep venous thrombosis; HIT, heparin-induced thrombocytopenia; IV, intravenous; PE, pulmonary embolism; SC, subcutaneously.

DVT prophylaxis decreases the incidence of PE and venous thromboembolism in the ICU patient. In general, all patients in the ICU should receive pharmacologic and/or mechanical DVT prophylaxis if no contraindication exists.

Arterial Thromboembolism

Acute arterial thrombosis can be secondary to embolization of material (eg, from the atria in atrial fibrillation or from a proximal source secondary to a damaged artery) or an in situ formation of clot. Symptoms are generally related to the territory served by the

artery that has thrombosed and generally is noted as a painful, pale, and cool extremity, or an acute neurologic deficit in the case of a stroke. However, in the ICU setting, these symptoms may be masked by the patient's comorbidities.

Clues from the physical examination can yield evidence as to the source of the thrombosis. Multiple sites of ischemia are typical of an embolic phenomenon (however can also be seen in the setting of vasculitis), whereas isolated ischemia is more typical of in situ thrombosis. Further evaluation of suspected arterial thrombosis can be performed with Doppler signal assessment and compression ultrasound, although computed tomographic angiography (CTA) can be more anatomically revealing and helpful.

Treatment of suspected arterial thrombosis should be instituted immediately, as delay in treatment can result in irreversible damage due to tissue ischemia. Anticoagulation should be initiated as outlined in Tables 68.3 and 68.4, and surgical or percutaneous interventionalist consultation should be sought for possible operative management.

Hypercoagulability Evaluation

Patients in the ICU have many transient risk factors for the development of thromboembolic disease. Because of this, most instances of thromboembolism do not warrant workup for an underlying hypercoagulable state. The optimal time for laboratory evaluation of hypercoagulable states is unclear but is often undertaken approximately 6 weeks to 6 months after the event. Laboratory evaluation in the immediate days to weeks following a thrombosis can yield false results because of the increase in acute-phase reactants associated with acute clot formation, which can result in false-positive tests for hypercoagulable states. However, in the setting of recurrent or atypical thrombosis, such as cerebral vein or visceral vein thrombosis and nonembolic arterial thrombosis, further evaluation is warranted. Minimal workup should include evaluation for HIT, lupus anticoagulant, anticardiolipin antibody, and

fasting plasma homocysteine level. In cases marked by recurrent thrombosis or cerebral or visceral vein thrombosis, further workup should include a prothrombin G20210A mutation analysis, paroxysmal nocturnal hemoglobinuria (PNH) testing, as well as a factor V Leiden mutation analysis. Hematology consultation should be obtained for further evaluation and long-term treatment planning.

Conditions Associated With Decreased Platelets and Hypercoagulability

There are occasional conditions that present with thrombocytopenia as well as hypercoagulability. HIT is a serious condition manifested by the formation of antibodies to platelets in response to heparin administration. This condition can cause thrombosis in the setting of severe thrombocytopenia and is discussed in detail in Chapter 65, Traumatic Brain Injury and Elevated Intracranial Pressure.

Thrombotic thrombocytopenic purpura is another condition associated with hypercoagulability and thrombocytopenia. This serious condition is the result of a deficiency of or inhibitor to the von Willebrand factor–cleaving protease, ADAMTS 13. It is manifested by thrombocytopenia, microangiopathic changes on peripheral blood smear (schistocytes), fever, mental status changes, and varying degrees of renal insufficiency. Treatment is emergent and requires immediate hematology consultation and plasma exchange. This condition is discussed further in Chapter 65, Acute Spinal Cord Disorders.

Disseminated intravascular coagulation can also present with thrombocytopenia and coagulopathy in the setting of hypercoagulability. Underlying conditions such as sepsis, ischemia, acidosis, and multiorgan failure can induce a consumptive coagulopathy, resulting in the formation of diffuse thrombi as well as diffuse hemorrhage.

69 Critical Care Rheumatology

Mohamed H. Babiker-Mohamed and Vladimir N. Despotovic

Intensive care unit (ICU) admissions due to rheumatologic conditions are not very common, but when they occur, they are often complex with multisystem involvement. Rapid diagnosis of the condition and initiation of treatment can minimize morbidity and mortality in this patient population in the ICU. In addition to the appropriate initial diagnostic workup and initiation of treatment, early consultation with the rheumatology service and other affected organ system-specific consultants can optimize the management and follow-up of these often-complicated patients.

General Rules

1. The most common cause of ICU admission for patients with rheumatologic illnesses is infection. The second most common cause is exacerbation or complications due to their underlying autoimmune disease.
2. The most common rheumatologic conditions in the ICU include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc).
3. The most likely cause of fever in patients with a rheumatologic diagnosis is infection.
4. All serologic testing must be interpreted in the context of the patient's clinical condition.
5. Inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are acute phase reactants and are nonspecific in the critical care setting.
6. Caution should be exercised in the intubation of patients with RA, particularly seropositive, erosive RA. Anterior atlantoaxial subluxation of C1 on C2 may occur, compressing the anterior spinal cord. Hyperextension of the neck during intubation could result in quadriplegia. If no previous C-spine imaging is available, inline stabilization of the spine should be done. Alternatively, endotracheal intubation with fiber-optic guidance can be performed.

7. Cricoarytenoid joint disease may cause difficulties during intubation in a patient with RA, presenting as hoarseness, inspiratory stridor, dyspnea, or wheezing.
8. Subglottic stenosis and tracheobronchomalacia can be observed in patients with relapsing polychondritis and, to a lesser degree, in those with antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis.
9. Cognitive impairment or coma without focal neurologic signs is rarely related to central nervous system (CNS) vasculitis.
10. Septic arthritis is a medical emergency, and if suspicion is high, arthrocentesis should be promptly pursued.
11. Steroid dosing:
    - To treat RA flares, a dose equivalent to 20 mg of prednisone daily is usually adequate.
    - In patients experiencing an acute gout flare when nonsteroidal anti-inflammatory drugs (NSAIDs)/colchicine are contraindicated, prednisone at 40 to 60 mg daily with a quick taper over 7 to 10 days is appropriate. Another option is prednisone 40 mg daily for 5 days without a taper.
    - A mild SLE or vasculitis flare usually responds to prednisone at 40 mg daily, followed by a 2-week taper.
    - For a moderate SLE or vasculitis flare, higher doses of steroids are required. Prednisone at 1 mg/kg/d (up to 60-80 mg/d) with a taper over 2 to 4 weeks is usually required. This will also necessitate an adjustment to the patient's chronic immunosuppressive therapy.
    - In severe, life-threatening SLE or vasculitis, high doses of intravenous glucocorticoids are preferred (methylprednisolone 500-1,000 mg IV daily for 3-5 days), followed by oral or parenteral therapy with dosing equivalent to 1 mg/kg of prednisone per day.
    - In severe, life-threatening illness with a strong suspicion of an autoimmune etiology, therapeutic intervention should not be delayed. Once infection has been reasonably excluded, empiric glucocorticoids can be initiated, and rheumatology or other appropriate service(s) can be consulted.
    - Patients who have been chronically on corticosteroids (even if none currently) will require stress dose steroids (hydrocortisone 50 mg IV every 6 hours or equivalent) during critical illness or surgical procedures to prevent shock and acute adrenal insufficiency.

Pulmonary Renal Syndrome and Diffuse Alveolar Hemorrhage

Pulmonary renal syndrome (PRS) is a combination of diffuse alveolar hemorrhage (DAH) and rapidly progressive glomerulonephritis (RPGN) (Table 69.1).

TABLE 69.1 Causes for Pulmonary Renal Syndrome and DAH

ANCA-Associated Vasculitis	Isolated DAH
Granulomatosis with polyangiitis (GPA) (Wegener granulomatosis)	Idiopathic pulmonary hemosiderosis
Microscopic polyangiitis (MPA)	Isolated pulmonary capillaritis
Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome)	**Other Causes**
Other Autoimmune Etiologies	Coagulopathies, including DIC and iatrogenic
Anti-GBM disease (Goodpasture syndrome)	Thrombocytopenia, including ITP
Antiphospholipid antibody syndrome (APS)	Thrombotic microangiopathy (TMA), including TTP and HUS
Systemic lupus erythematosus (SLE)	Hematopoietic cell transplantation
Systemic sclerosis (SSc)	Infections (particularly in the setting of coagulopathy)
Idiopathic inflammatory myopathies (IIMs)	Drugs
Henoch-Schönlein purpura (HSP)	ARDS (particularly in the setting of coagulopathy)
Cryoglobulinemia	Mitral stenosis
Behcet syndrome	Pulmonary infarct
IgA nephropathy	Acute interstitial pneumonia (AIP)
Rheumatoid arthritis	Radiation pneumonitis
Pauci-immune glomerulonephritis	Infective endocarditis

ANCA-Associated Vasculitis	Isolated DAH
Mixed connective tissue disease	

ANCA, antineutrophilic cytoplasmic antibody; ARDS, acute respiratory distress syndrome; DAH, diffuse alveolar hemorrhage; DIC, disseminated intravascular coagulation; GBM, glomerular basement membrane; HUS, hemolytic uremic syndrome; IgA, immunoglobulin A; ITP, immune thrombocytopenia; TTP, thrombotic thrombocytopenic purpura.

When to Suspect. Diffuse pulmonary infiltrates, anemia, and low-grade fevers in the setting of hematuria, red blood cell (RBC) casts, and acute renal failure.

Clinical Findings. Hemoptysis (absent in 30% of DAH), purpuric rash, active urinary sediment (RBC casts most specific but often not present), renal impairment, decrease in hemoglobin (Hb) levels, arthralgias/arthritis, mononeuritis multiplex, pericarditis/myocarditis/pleuritis, sinusitis, and cerebral ischemia.

Investigation

1. Labwork: Complete blood count with Hb and platelets, basic coagulation tests, hemolysis labs including a peripheral blood smear, blood urea nitrogen (BUN) and Cr levels, urinalysis, spun urine sediment assessment, and serologies including antinuclear antibody (ANA), ANCA, and anti-glomerular basement membrane (anti-GBM). Also consider rheumatoid factor (RF)/anticyclic citrullinated peptide (anti-CCP) and myositis panel.
2. Imaging: Chest radiograph and/or chest computed tomography (CT) scan.
3. Procedures: Flexible bronchoscopy with bronchoalveolar lavage (BAL). BAL return should reveal increasingly bloody returns on subsequent passes through a wedged bronchoscope. BAL should be sent for an infectious workup to rule out infection as the cause of DAH. Biopsy is usually not necessary. Percutaneous renal biopsies with histopathology and immunohistochemistry can finalize the diagnosis and are higher yield than transbronchial lung biopsies.

Management. Treat the underlying condition, maintain adequate oxygenation, provide ventilatory support if needed with adequate positive end–expiratory pressure (PEEP), and correct any coagulopathies. If an autoimmune condition is suspected and no active infection is found, consider pulsed-dose steroids (methylprednisolone 1,000 mg daily for 3 days) followed by high-dose steroids (methylprednisolone 1 mg/kg daily or equivalent). Additional treatment options to consider include plasmapheresis, intravenous immune globulin (IVIG), or

specific immunosuppression depending on the condition and diagnosis. If available, assess for extracorporeal membrane oxygenation (ECLS) in appropriate candidates with difficulty oxygenating. The presence of bleeding and the potential need for anticoagulation should not be considered an absolute contraindication to ECLS support.

Critical Complications of Autoimmune Diseases

SYSTEMIC LUPUS ERYTHEMATOSUS

- SLE is a chronic autoimmune disease with the potential to affect all organ systems. SLE activity markers (Table 69.2) are useful for determining disease status. Acute life-threatening complications are overall rare, with the most common manifestations including:
  - CNS complications: Aseptic meningitis, cerebritis, seizures, and stroke in patients with SLE with altered mental status. Spinal cord involvement manifests as transverse myelitis, presenting with bilateral progressive weakness and sensory alterations.
  - Pulmonary system complications: DAH (see aforementioned) and pulmonary embolism (PE).
  - Hematologic system complications: Immune thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), and antiphospholipid syndrome (APS) testing should be considered in thrombocytopenic patients. In addition, infectious and iatrogenic etiologies should be suspected. In cases with marked cytopenia of two- or three-cell lineages, especially if associated with a fever, macrophage activation syndrome (MAS) should be suspected. MAS (hemophagocytic lymphohistiocytosis [HLH] in the setting of certain rheumatologic disorders) is a rapidly progressive and life-threatening syndrome associated with elevated levels of ferritin, triglycerides, liver function tests (LFTs), and lactate dehydrogenase (LDH), as well as low haptoglobin and fibrinogen levels. Elevated soluble CD25 (sIL-2 receptor) and hemophagocytosis on bone marrow biopsy are classically seen. Suspicion and early diagnosis are key to a better outcome.
  - Cardiovascular system: In patients with SLE with heart failure symptoms, consider myocarditis, valvular vegetations (Libman-Sacks), tamponade, premature atherosclerosis, or pulmonary hypertension.
  - Gastrointestinal system: For unexplained abdominal pain in SLE, consider mesenteric ischemia or vasculitis.

TABLE 69.2 Systemic Lupus Erythematosus (SLE)

Antinuclear Antibodies (ANAs): If negative, patient is extremely unlikely to have SLE. Positive test is only useful if within the proper clinical scenario. Only 5% of the general population with positive ANA has SLE. Increased incidence of positive ANA with increased age, certain medications, malignancies, infections, and other autoimmune disorders.
Anti–Double-Stranded DNA Antibodies (dsDNA) Very specific for SLE at moderate-to-high titers
Extractable Nuclear Antigen Antibodies (ENAs):
Anti-Sm (Anti-Smith): Nearly 100% specific for SLE
Anti-Ro (SSA):

- Associated with Sjögren syndrome (70%)
- Heart block in children with SSA-positive mothers
- Associated with subacute cutaneous lupus erythematosus (SCLE)

Anti-La (SSB): Sjögren syndrome
Ribonucleoprotein (RNP): High-titer anti–U1-RNP antibodies in association with overlapping clinical features of SLE, systemic sclerosis (SSc), and polymyositis (PM) are seen in mixed connective tissue disease (MCTD)

Lupus Flare:

- Associated with elevated anti-dsDNA, low C3 and C4. These tests may correlate with disease activity, mainly with nephritis. Comparison to previous titers during low disease activity as well as disease flares can be helpful and can vary among different patients. Disease activity association with the anti-dsDNA, C3 and C4 tends to follow similar trends in individual patients.
- Urinalysis with urine microscopy and protein/creatinine ratio should be checked with suspected lupus nephritis.
- In anemic patients, hemolysis should be suspected and direct Coombs antibody test and evaluation for lupus-associated microangiopathic hemolytic anemia (MAHA) should be done.
- In thrombocytopenic patients, ITP, TTP, and APS testing in addition to suspecting infectious and iatrogenic etiologies.

APS, antiphospholipid syndrome; ITP, immune thrombocytopenia; LDH, lactate dehydrogenase; LFT, liver function test; PPT, partial thromboplastin time; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura.

Vasculitis

The inflammation of vessel walls that occurs with the vasculitides affects vessels of different sizes depending on the specific type of vasculitis. (Figure 69.1)

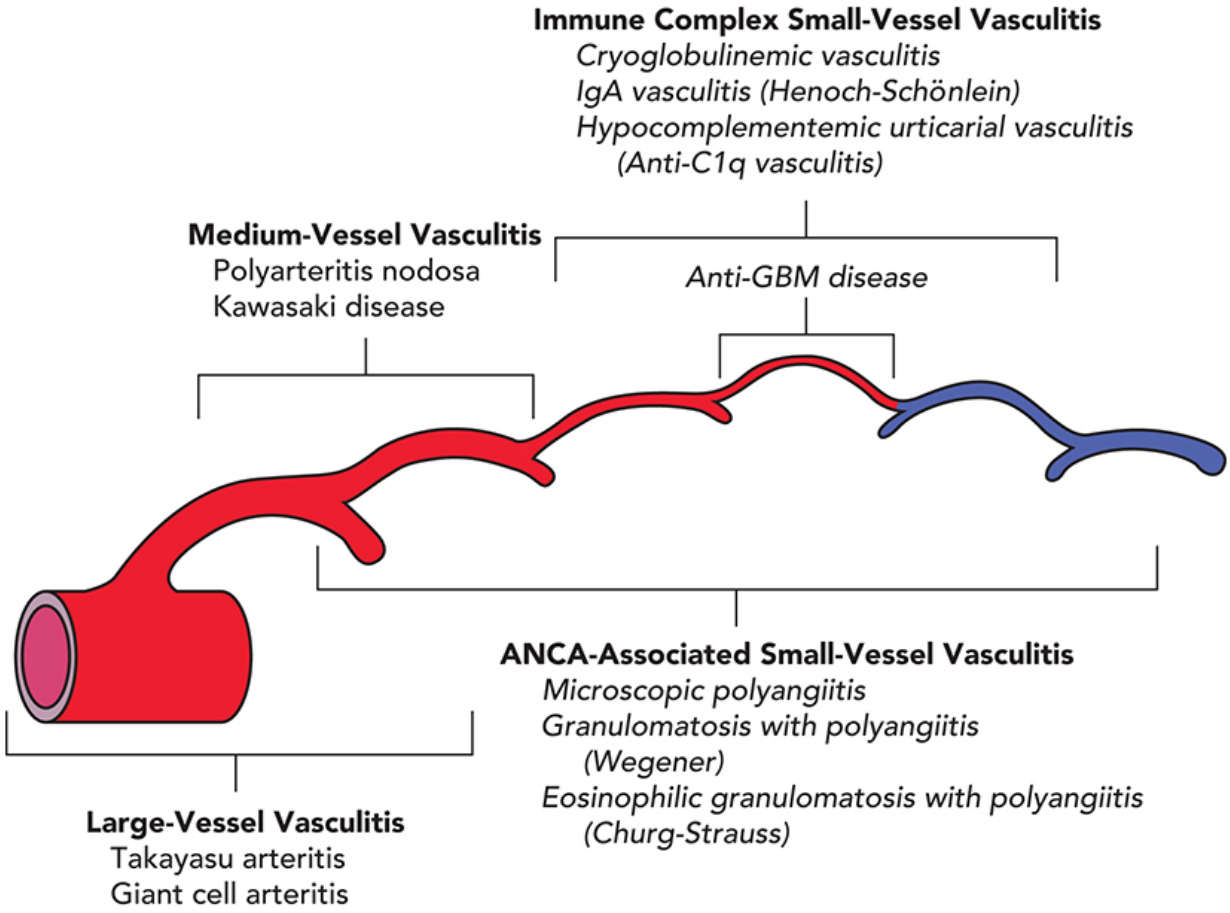


FIGURE 69.1 **Predominant types of vessels affected by major categories of systemic vasculitis**. ANCA, antineutrophilic cytoplasmic antibody; GBM, glomerular basement membrane; IgA, immunoglobulin A. Reproduced with permission from John Wiley & Sons, Inc. © Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.

LARGE-VESSEL VASCULITIS

Giant Cell Arteritis

The most common systemic vasculitis, with a lifetime risk of 1% in women and 0.5% in men (Table 69.3).

TABLE 69.3 **Giant Cell Arteritis**

Risk Factors	Clinical Manifestations	Treatment

Risk Factors	Clinical Manifestations	Treatment
• Age >50 y, peak 70-80 y • Scandinavian ethnicity, less common in Hispanics, Asians, and Mediterranean populations and least common in African Americans • Females have greater incidence than males. • Polymyalgia rheumatica (PMR) • Family history	• Systemic symptoms, including fever, weight loss, and fatigue • Presence of PMR • Headache • Jaw claudication • Cranial ischemic events, including transient and permanent vision loss with classic ophthalmologic findings (anterior or posterior ischemic optic neuropathy or central retinal artery occlusion) • Large-vessel vasculitis on imaging or pathology • Elevated ESR and CRP • Temporal artery tenderness or pulselessness • Imaging changes on MRI/MRA, ultrasonography, or PET imaging • Temporal artery biopsy with necrotizing arteritis or granulomatous inflammation with multinucleated giant cells	• High-dose steroids should be initiated early. • If the suspicion is high, treatment with steroids should be initiated before the diagnosis is confirmed. Temporal artery biopsy remains diagnostic for up to 2 wk after steroid therapy. • If ischemic symptoms are present, 1 mg/kg of prednisone or methylprednisolone daily should be started and pulse dose of methylprednisolone of 1 g/d × 3 d should be considered. • If no ischemic symptoms are present, lower initial doses of 40 mg/d prednisone can be considered. • Start taper after 2-4 wk. • Consider low-dose daily aspirin 81-100 mg. • In acute treatment failures, consider cyclophosphamide. • Consider tocilizumab as adjunct treatment to high-dose steroids based on the GiACTA study.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GiACTA, Giant Cell Arteritis Actemra; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PET, positron emission tomography.

SMALL-VESSEL VASCULITIS

Antineutrophilic Cytoplasmic Antibody-Associated Small-Vessel Vasculitis

- **Clinical Features of ANCA Vasculitis** (Table 69.4, Figure 69.2)

- **Additional considerations in ANCA-associated vasculitis:**
  - The Rituximab in ANCA-Associated Vasculitis (RAVE) trial showed similar outcomes between cyclophosphamide and rituximab in nonintubated patients with serum creatinine less than 4. Lower-quality data support the use of rituximab without the aforementioned exclusions.
  - The maintenance of remission using rituximab in systemic ANCA-associated vasculitis (maintenance of remission using rituximab in systemic ANCA-associated vasculitis (MAINRITSAN)) trial and its long-term follow-up study showed rituximab's superiority to azathioprine in maintaining remission and improving long-term survival.
  - The (plasma exchange and glucocorticoids in severe ANCA-associated vasculitis (PEXIVAS) trial showed that plasma exchange did not reduce the incidence of death or end-stage renal disease (ESRD). Lower-quality data showed favorable outcomes in patients at high risk of ESRD or on RRT (renal replacement therapy) or with DAH. Plasma exchange should not be done routinely, and the risks and benefits should be considered in individual patients.

TABLE 69.4 Clinical Features of ANCA-Associated Vasculitis

	Granulomatosis With Polyangiitis (GPA) (Wegener Granulomatosis)	Microscopic Polyangiitis	Eosinophilic Granulomatosis With Polyangiitis (EGPA) (Churg-Strauss Syndrome)
ANCA positive	80%-90%	70%	50%
ANCA type	PR3 > MPO	MPO > PR3	MPO > PR3
Pulmonary	DAH, nodules, cavitary lesions, infiltrates	DAH	DAH, infiltrates, asthma
Renal	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis	Segmental necrotizing glomerulonephritis
Ophthalmologic	Scleritis, episcleritis, uveitis	Rare: Scleritis, episcleritis, uveitis	Rare: Scleritis, episcleritis, uveitis
ENT	Saddle nose deformity, subglottic stenosis, hearing loss	Hearing loss	Allergic rhinitis, nasal polyps, hearing loss

	Granulomatosis With Polyangiitis (GPA) (Wegener Granulomatosis)	Microscopic Polyangiitis	Eosinophilic Granulomatosis With Polyangiitis (EGPA) (Churg-Strauss Syndrome)
Cardiac	Rare: Myocarditis, valvular lesions	Rare: Myocarditis	Myocarditis
Neurologic	CNS vasculitis, mononeuritis multiplex—occasional	CNS vasculitis, mononeuritis multiplex—common	CNS vasculitis, mononeuritis multiplex—very common
Pathology	Leukocytoclastic vasculitis, granulomas	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis, eosinophilic granulomas/infiltrates

ANCA, antineutrophilic cytoplasmic antibody; CNS, central nervous system; DAH, diffuse alveolar hemorrhage; ENT, ear, nose, and throat; MPO, myeloperoxidase; PR3, proteinase 3.

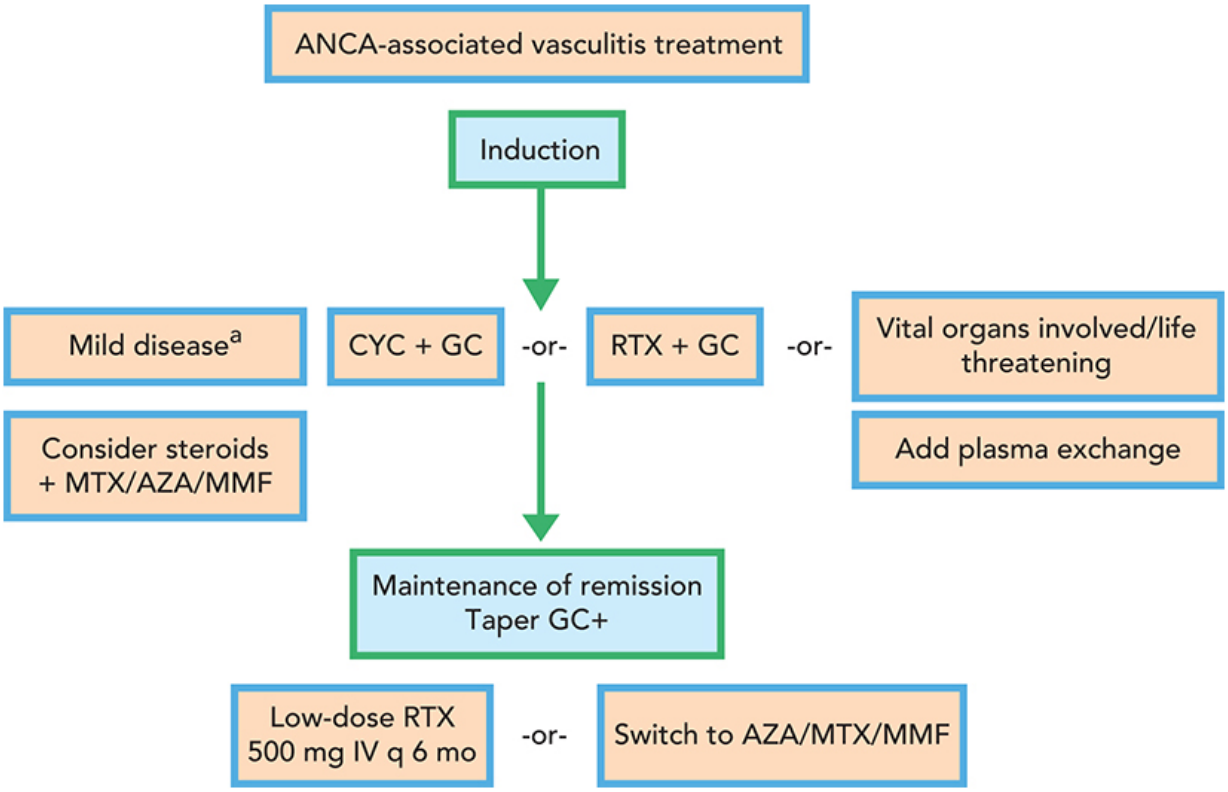


FIGURE 69.2 **ANCA-associated vasculitis**. [a]Not life- or organ-threatening disease. ANCA, antineutrophilic cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; MMF, mycophenolate; MTX, methotrexate; RTX, rituximab.

Catastrophic Antiphospholipid Syndrome

Catastrophic antiphospholipid syndrome (CAPS) is a rapidly progressive, life-threatening disease that causes multiorgan thromboses and dysfunction in the presence of antiphospholipid antibodies.

When to Suspect. Rapid multiorgan thromboses, especially in the setting of SLE, infections, or known APS. An elevated partial thromboplastin time (PTT) that does not correct with a 50:50 mixing study of patient plasma with normal plasma in the right clinical setting—particularly in the setting of a clot—is also suggestive of the presence of an inhibitor and APS. Certain anticoagulant medications will alter the testing.

Catastrophic Antiphospholipid Syndrome Features
It can be difficult to distinguish CAPS from other disease processes that can lead to multiorgan thrombotic events, such as hemolytic uremic syndrome (HUS), TTP, and DIC (Table 69.5).

TABLE 69.5 CAPS Features

Organ System Involved	Clinical Features
Heart	Cardiac valve thickening/sterile endocarditis
Lungs	Pulmonary emboli, diffuse alveolar hemorrhage, ARDS
CNS	Cerebrovascular accidents
Viscera	Visceral ischemia
Other	Venous or arterial clot, especially atypical

ARDS, acute respiratory distress syndrome; CAPS, catastrophic antiphospholipid syndrome; CNS, central nervous system.

Catastrophic Antiphospholipid Syndrome Diagnostic Criteria and Management

- High suspicion, early diagnosis, and aggressive therapy are essential (Table 69.6)
- Treat any possible underlying infection
- Anticoagulation with heparin
- Plasma exchange for five consecutive days with or without IVIG (400 mg/kg/d for 5 days) after plasma exchange has been completed.
- Pulse dose of systemic glucocorticoids (methylprednisolone 1 g IV daily for 3 days), followed by high-dose oral or parenteral therapy (prednisone 1 mg/kg

daily; usually do not exceed 60-80 mg).

- In refractory cases of CAPS, rituximab and eculizumab have also been used in addition to standard cyclophosphamide therapy.

TABLE 69.6 CAPS Diagnostic Criteria

Evidence of involvement of three or more organs, systems, or tissues
Manifestation development simultaneously or in <1 wk
Histopathologic confirmation of small-vessel occlusion in at least one organ or tissue
Laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and/or anti–beta$_2$-glycoprotein I antibodies)
Definite CAPS: All criteria met
Probable CAPS: Absence of second OR third criterion, or two organs/systems involved

CAPS, catastrophic antiphospholipid syndrome.

Guidance to Laboratory Test Interpretation and Key-Associated Facts

Scleroderma Renal Crisis (Table 69.7)
Systemic Lupus Erythematosus (SLE) (Table 69.2)
Vasculitis (Table 69.8)
Antiphospholipid Antibody Syndrome (Table 69.10)
Systemic Sclerosis (SSc) (Scleroderma) (Table 69.9)
Arthrocentesis (Table 69.11)
Interpretation of Synovial Fluid Findings (Table 69.12)
Rheumatoid Arthritis (Table 69.13)
Myositis (Table 69.14)

TABLE 69.7 Scleroderma Renal Crisis

Risk Factors	Clinical Manifestations	Management

Risk Factors	Clinical Manifestations	Management
• Scleroderma particularly with diffuse skin involvement (up to 20%) • Palpable tendon friction rubs • Antibodies to RNA polymerase III • Use of systemic glucocorticoids	• Abrupt onset of severe hypertension • Acute onset, rapidly progressive renal failure • Microangiopathic hemolytic anemia and thrombocytopenia • Urinalysis can range from normal to mild proteinuria to abundant cells and casts (glomerulonephritis is not a feature).	• Antihypertensives, need to always include ACE inhibitors even in the setting of acute kidney injury and a rising creatinine • Supportive measures

ACE, angiotensin-converting enzyme.

TABLE 69.8 Vasculitis

C-ANCA/P-ANCA	High-titer anti-PR3 (proteinase 3) antibody is extremely specific (>95%).
Complement	Low-serum complement levels are usually present in mixed cryoglobulinemia and SLE.
Rheumatoid factor	High titers seen in rheumatoid arthritis/Sjögren syndrome and cryoglobulinemia-associated vasculitis
Additional workup	Cryoglobulins, hepatitis B and C, serum protein electrophoresis and immunofixation, and antiglomerular basement membrane antibody Strongly consider an angiographic study or biopsy if diagnosis not clear and with clinical suspicion of vasculitis.

C-ANCA, cytoplasmic antineutrophilic cytoplasmic antibody; P-ANCA, perinuclear antineutrophilic cytoplasmic antibody; SLE, systemic lupus erythematosus.

TABLE 69.9 Systemic Sclerosis (SSc) (Scleroderma)

Anti-Scl 70 (topoisomerase)	**Diffuse** disease. Classically skin involvement proximal to the elbows. Can progress rapidly, can have severe interstitial lung disease (ILD)
Anticentromere	**Limited** disease (CREST syndrome—calcinosis, Raynaud phenomenon,

antibody	esophageal dysmotility, sclerodactyly, telangiectasias). Associated with pulmonary hypertension and digital ischemia
Anti-polymerase III	**Diffuse** disease, scleroderma renal crisis, GAVE (gastric antral vascular ectasia)
ANA	Present in 95% of SSc, classically with nucleolar of centromere pattern

ANA is present in vast majority of patients with SSc (95%), and Raynaud phenomenon is almost universal. The suspicion of SSc should be dependent on the presence of both.

ANA, antinuclear antibody

TABLE 69.10 Antiphospholipid Antibody Syndrome

IgG and IgM anticardiolipin antibodies (aCL)
IgG and IgM anti–beta$_2$-glycoprotein (GP) I antibodies
Lupus anticoagulant testing
Additional testing: 50:50 plasma mixing study as described earlier under CAPS does not substitute for the formal testing but can provide a rapid test to increase the suspicion for the presence of the inhibitor.

CAPS, catastrophic antiphospholipid syndrome; IgG, immunoglobulin G; IgM, imunoglobulin M.

TABLE 69.11 Arthrocentesis—Indications and Fluid Testing

Acute monoarthritis
Suspicion for infection, crystal-induced arthritis, or hemarthrosis
Joint effusion in the setting of trauma
Joint effusion with uncertain diagnosis

TABLE 69.12 Interpretation of Synovial Fluid Findings

	Noninflammatory	Inflammatory	Septic	Hemorrhagic
Appearance	Clear/yellow/viscous	Cloudy/yellow	Opaque/varies	Opaque/red
WBC/mL	0-2,000	>2,000	>20,000	0-2,000
PMNs	<25%	>50%	>75%	50%-75%
Crystals	Absent	Present in gout and pseudogout	Absent	Absent

	Noninflammatory	Inflammatory	Septic	Hemorrhagic
Comment	Normal/osteoarthritis	Gout, pseudogout, SLE, RA, spondyloarthropathy	Positive Gram stain and culture	High RBCs

PMN, polymorphonuclear leukocyte; RA, rheumatoid arthritis; RBC, red blood cell; SLE, systemic lupus erythematosus; WBC, white blood cell.

TABLE 69.13 Rheumatoid Arthritis

RF (rheumatoid factor)	More sensitive (75%), less specific (75%)
Anti-CCP antibody (anticyclic citrullinated peptide)	More specific (95%), less sensitive (65%)

TABLE 69.14 Myositis

Creatine kinase (CK), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH (lactate dehydrogenase) (isolated elevation in aldolase may be suggestive of perimysial disease)
Anti–Jo-1 antibody (most common, more rapid result), and myositis-specific antibody panel (includes Jo-1)
EMG/NCS (electromyogram/nerve conduction studies)
Muscle biopsy, helpful if site identified with magnetic resonance imaging (MRI)/ultrasound
Inflammatory arthritis, skin involvement, and interstitial lung disease (ILD) are also commonly present.

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70 Management of the Solid Organ Transplant Recipients in the Intensive Care Unit

Nnamdi Anunobi, Chad A. Witt, and Rodrigo Vazquez Guillamet

The number of solid organ transplants (SOTs) performed worldwide continues to increase annually. In 2021, over 144,000 transplants were performed, with renal being the most common (64.1%), followed by liver (24%), heart (5.8%), lung (4.5%), and pancreatic (<2%) transplants. Moreover, the overall survival for most SOT recipients has been improving, owing to ongoing improvements in surgical techniques and longitudinal medical management of SOT recipients. As a result, it is increasingly likely to encounter SOT recipients in various clinical settings, including the intensive care unit (ICU). Most indications for ICU care in SOT recipients are multifactorial; however, from a practical perspective, it is useful to classify them into infectious, immunosuppressive-related, and anatomic/surgical complications.

Infectious Complications

Infectious complications are the leading cause for ICU admission after SOT. Infection risk is determined by the net level of immunosuppression and the use of prophylactic strategies against bacterial, viral, and fungal pathogens. In general, the degree of immunosuppression is most intense in the first 6 to 12 months posttransplantation. SOT recipients may receive perioperative induction therapy with T-cell– or B-cell–depleting agents (eg, alemtuzumab, antithymocyte globulin), which can lead to profound and prolonged immunosuppression potentially lasting for several

months. In the early (≤1 month) postoperative period, the site of infection often involves the transplanted organ (eg, mediastinitis in heart recipients, intra-abdominal infection in liver and kidney recipients, airway infection, pneumonia, or pleural infections in lung recipients). In addition, infections related to the surgical site, wound dehiscence, or anastomotic leaks are often encountered. Nosocomial infections with multidrug resistant (MDR) organisms such as MRSA, VRE, and MDR gram-negative organisms are also common. Donor- or recipient-derived infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Aspergillus* infections are also traditionally seen early in the posttransplant course. However, with increasing use of prophylaxis against infections such as CMV, *Pneumocystis jirovecii,* and *Aspergillus* spp., these infections can be seen later in the course after prophylactic antimicrobials are discontinued. Opportunistic infections such as CMV, toxoplasmosis, *P. jirovecii*, *Cryptococcus*, mycobacteria, herpes simplex virus (HSV), varicella-zoster virus (VZV), EBV, *Listeria*, and *Nocardia* tend to occur within the first 6 to 12 months posttransplantation. After 6 months, community-acquired infections, including community-acquired pneumonia (CAP) and urinary tract infections (UTIs), predominate. Opportunistic infections, earlier described, can also be seen in this period due to chronic suppression of T-cell immunity. Although highest early in the posttransplant course, the risk of infectious complications continues lifelong, given the chronic, ongoing immunosuppression that SOT recipients require. Please refer to Chapter 40, Cellulitis/Fasciitis/Myositis, for further reading on infections in SOT recipients. Table 70.1 summarizes common ICU indications of infectious and noninfectious etiology.

TABLE 70.1 Common Intensive Care Unit (ICU) Syndromes in Solid Organ Transplant Recipients

Syndrome	Clinical Presentation	Diagnostic Testing	Management

Syndrome	Clinical Presentation	Diagnostic Testing	Management
Acute hepatic artery thrombosis	Liver: sudden sharp rise in liver enzymes	1-4 wk posttransplant Doppler ultrasound, angiogram	Emergent surgical repair; endovascular thrombectomy and stenting; retransplantation
Subacute/chronic hepatic artery thrombosis	Bile leak; biliary sepsis, peritoneal infections	Computed tomography, cholangiography (retrograde, magnetic, etc)	Stenting; broad-spectrum antibiotics plus drainage; retransplantation
Renal artery thrombosis	Renal: acute kidney injury, nausea, vomiting	Renal ultrasound with Doppler; angiography	Thrombectomy plus stenting
Ischemic airway injury with airway obstruction	Dyspnea, sudden and severe when complete obstruction is present	Computed tomography with contrast, intubation and bronchoscopy	Bronchoscopy with therapeutic aspiration of necrotic material, with/without debridement, balloon dilation, or stenting when dehiscence is present. Broad-spectrum antibiotics
Pulmonary embolism (any SOT)	Dyspnea, shock, chest pain. Lung transplant recipients have higher incidence of lung infarction.	Computed tomography with contrast	Anticoagulation; perioperatively and high bleeding risk venous filters and supportive care

Syndrome	Clinical Presentation	Diagnostic Testing	Management
Hypertensive emergency and urgency (any SOT)	Headache, renal failure, altered mentation	CNI blood levels, Doppler ultrasound in renal transplants	CNI change after brief discontinuation (if PRES). Aggressive BP control; renal artery repair
Acute on chronic respiratory failure (lung transplant)	Dyspnea, weight loss, history of declining lung function	Bacterial, fungal and viral cultures for contributing infections	Supportive care with attention to obstructive lung physiology. Antibiotics and steroids
Sepsis and septic shock	Most commonly related to transplanted organ or pneumonia	Please refer to Chapter 40	Please refer to Chapter 40

BP, blood pressure; CNI, calcineurin inhibitor; SOT, solid organ transplant.

Complications of Immunosuppressive Therapy

Immunosuppression is divided into three main periods: induction, maintenance, and treatment of acute rejection. Table 70.2 summarizes the common drugs for each indication. Two aspects of immunosuppression are relevant to ICU management: (1) dose adjustment during critical illness and (2) drug-related toxicities as an indication for ICU care.

TABLE 70.2 Classes of Immunosuppressive Drugs

Induction					
Class	**Name**	**Mechanism of Action**	**Interactions**	**Notes**	**Monitoring**
Monoclonal	IL-2 antagonists, eg, basiliximab, alemtuzumab	Monoclonal antibodies that block T lymphocyte IL-2 receptor complex (basiliximab) or CD52 antigen expression of T and B cells (alemtuzumab)	No significant interactions	Wide range of side effects in the acute setting, most notably hypertension. Serious, fatal infusion reaction occur with alemtuzumab	Alemtuzumab-CBC, infusion reactions
Polyclonal	Anti-lymphocyte and anti-thymoglobulin	Antibodies directed against T-cell antigens causing rapid depletion of T-lymphocytes		Serum sickness, dose-dependent leukopenia, and thrombocytopenia	CBC

Maintenance						
Class	**Name**	**Mechanism of Action**	**Toxicity**	**Interactions**	**Notes**	**Monitoring**
Corticosteroids	Prednisone, prednisolone, methylprednisolone	Multifactorial; cause redistribution of leukocytes; inhibit proliferation of T cells; decrease synthesis of prostaglandins, proinflammatory cytokines, leukotrienes	Hyperglycemia, hypertension, osteopenia, avascular necrosis of bone, impaired wound healing, adrenal suppression	No significant interactions	Wide range of side effects, in the acute setting, most notably hyperglycemia and hypertension	None
Calcineurin inhibitors	Tacrolimus	Binds to FKBP, forming a complex that inhibits calcineurin that leads to decreased transcription of cytokines, such as IL-2, IL-3, and IFN-γ	Renal dysfunction, hypertension, hyperkalemia, hyperglycemia, diabetes, neurotoxicity (tremor, headaches), GI toxicity	Substrate and inhibitor of pGP and CYP3A4 Interacts with a wide array of drugs that induce or inhibit CYP3A4 Significant drug interaction with azoles dramatically increasing tacrolimus exposure	PO or sublingual route preferred over IV to minimize renal toxicity	Trough level; monitor renal function
	Cyclosporine	Same as above, binds to cyclophilin instead of FKBP	Renal dysfunction, hirsutism, tremor, hyperlipidemia, hyperplasia of gum, hyperuricemia	Substrate and a strong inhibitor of pGP; hepatically metabolized by CYP3A4; interacts with a wide range of drugs, including CCB, antifungals, antibiotics, glucocorticoids, PI grapefruit juice Significant drug interaction with azoles dramatically increasing tacrolimus exposure	Sandimmune and Neoral differ in their pharmacokinetics and should NOT be used interchangeably.	Two-hour peak and/or trough level, monitor renal function

Maintenance						
Class	**Name**	**Mechanism of Action**	**Toxicity**	**Interactions**	**Notes**	**Monitoring**
mTOR inhibitors	Sirolimus and everolimus	Bind to FKBP, inhibits mTOR that is involved in cell cycle proliferation	Delayed wound healing, anemia, leukopenia, thrombocytopenia, hypokalemia, oral ulcers, GI toxicity	Substrate of pGP and CYP3A4; monitor carefully when coadministered with other CYP3A4 substrates Concomitant administration with cyclosporine may aggravate renal dysfunction, myelosuppression and hyperlipidemia Significant drug interaction with azoles dramatically increasing drug level	Not used early (<3 mo) in lung recipients due to airway dehiscence	Trough level
Selective T-cell costimulator blocker	Belatacept	Binds to CD80 and CD86, blocking CD28-mediated T-cell costimulation	Higher risk of rejection compared to cell cycle inhibitors. PTLD risk is increased. Use is contraindicated in EBV-mismatched recipients, leukopenia, higher severity of CMV disease.	No significant drug interactions. Clearance not dependent on liver or kidney function	In renal transplantation, it is associated with prolonged graft function despite more frequent rejection episodes. Higher mortality in liver and lung transplantation	White blood cell count
Antimetabolites	Mycophenolate mofetil and mycophenolic acid	Hydrolyzed to MPA, a selective inhibitor of IMPDH, an enzyme involved in the synthesis of guanine nucleotide in lymphocytes	GI toxicity (nausea, diarrhea), leukopenia, anemia, thrombocytopenia	MPA is metabolized to inactive MPAG, which is renally excreted. Coadministration with antiacids containing Mg or Al leads to decreased absorption of MMF Acyclovir and ganciclovir may compete with MPAG for tubular secretion resulting in increased blood levels of both the antiviral and MPAG	Mycophenolic acid is enteric-coated and may improve GI side effects compared to mycophenolate mofetil.	CBC
	Azathioprine	Converted to 6-MP, which is converted to metabolites that inhibit purine synthesis, inhibiting cell proliferation	Bone marrow suppression, leukopenia, thrombocytopenia, anemia, hepatotoxicity, alopecia, GI toxicity, pancreatitis	Partially metabolized by xanthine oxidase. Avoid concomitant use with xanthine oxidase inhibitor (eg, allopurinol) or dose decrease; coadministration with ACEi may aggravate myelosuppressive effect.	Low TPMT activity associated with higher risk of myelosuppression	CBC and LFTs

ACEi, angiotensin-converting enzyme inhibitor; CBC, complete blood count; CCB, calcium channel blocker; CMV cytomegalovirus; Cr, creatinine; FKBP, FK506-binding protein; GI, gastrointestinal; IMPDH, inosine monophosphate dehydrogenase; LFT, liver function test; 6-MP, 6-mercaptopurine; MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; pGP, P-glycoprotein; PI, protease inhibitors; TPMT, thiopurine methyltransferase.

There are three major classes of maintenance immunosuppressive agents most commonly used in SOT: (1) corticosteroids, (2) antimetabolic agents, and (3) calcineurin inhibitors (CNIs) (Table 70.2). Over time, the use of mammalian target of rapamycin (mTOR) inhibitors is also increasing.

In general, in the setting of severe infections, it is reasonable to hold antimetabolite agents (eg, mycophenolate mofetil and

azathioprine) until there is clinical improvement or resolution. They should also be held during episodes of leukopenia or neutropenia. CNIs are widely utilized in the maintenance therapy of SOT recipients, and chronic kidney disease due to calcineurin inhibitor nephropathy (CIN) is prevalent. Drugs should be renally dosed, and other nephrotoxic drugs and iodinated contrast should be used with caution. Mild neurotoxicity manifested by tremor is common in patients on CNI. Finally, chronic use of steroids leads to adrenal insufficiency, and stress dose steroids should be initiated early in patients in shock.

A common CNI-related ICU indication is posterior reversible encephalopathy syndrome (PRES), a condition clinically characterized by encephalopathy, headaches, seizure, and visual disturbances. A retrospective study from a large transplant center reported the rate of PRES to be 0.49% among all SOT recipients. While cyclosporine is the most commonly reported agent, PRES is also associated with tacrolimus and the mTOR inhibitor sirolimus. Diagnosis is made both clinically and with supporting neuroradiographic findings of symmetric vasogenic edema in the white matter, typically seen in the posterior cerebral hemispheres on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. Supratherapeutic levels of CNI are often but not always observed, and the treatment involves cessation of the inciting agent, aggressive blood pressure control, and switching immunosuppressive agents. SOT recipients who develop PRES on one CNI will often tolerate the other CNI without difficulty. CNI-associated PRES resolves in about 90% of patients, with 10% of patients recovering with some residual neurologic sequelae. Maintaining a high index of suspicion is the key in early diagnosis and treatment.

Microangiopathic hemolytic anemia (MAHA) in lung transplantation is most commonly related to the use of CNIs. Patients typically present with intravascular hemolytic anemia, consumptive thrombocytopenia, and renal failure. The differential includes primary MAHA and other secondary causes of MAHA (eg, pregnancy,

malignant hypertension). Treatment requires stopping CNI and switching to an alternative agent.

Thymoglobulin consists of polyclonal antibodies against T cells created from rabbits or horses. Both are associated with hypersensitivity reactions, cytopenias, immune complex–mediated glomerulonephritis, and serum sickness. Finally, mTOR inhibitors can present with hypoxemic respiratory failure secondary to different forms of lung toxicity, with the most common pattern of involvement being bilateral upper lobe interstitial infiltrates.

SOT recipients are also at risk for immunosuppression-related malignancies. In a large cohort study, the incidence of overall malignancy was 2 times that expected from an age- and region-adjusted cohort. In particular, malignancies associated with infectious etiology, including Kaposi sarcoma (human herpesvirus [HHV-8]), liver cancer (hepatitis B virus [HBV], hepatitis C virus [HCV]), non-Hodgkin lymphoma (EBV), and vulvar cancer (human papillomavirus [HPV]), showed the highest increase in incidence. On occasions, these malignancies will lead to ICU admission.

Anatomic or Surgical Concerns

Surgical/anatomic complications in SOT are common indications for ICU care in the early-posttransplant period, and some become sources of recurrent admissions (eg, ischemic cholangiopathy leading to recurrent cholangitis). Presentation follows easily recognizable syndromes (Table 70.1).

FINAL CONSIDERATIONS

The differential diagnosis of acute renal failure in renal transplant recipients includes allograft rejection, drug toxicity (eg, CNI, antibiotics), ATN (acute tubular necrosis), and BK virus nephropathy (BKVN). Differentiating between BKVN and allograft rejection is of particular importance since the treatment for each condition will drastically differ. In renal transplant recipients with hypertensive

urgency or emergency, transplant renal artery stenosis (TRAS) should be considered in the differential diagnosis. TRAS is a well-recognized complication, most commonly occurring during the first 6 months posttransplantation but can present at any time. While an arteriography remains the gold standard for diagnosis, MR or CT angiography, isotope renography, and renal Doppler ultrasonography are increasingly utilized due to their less invasive nature and substantial contrast load,. In addition, other factors contributing to hypertension must be considered, such as the use of CNI and glucocorticoids. ICU management should include assessment and stabilization of acute respiratory failure and control of blood pressure. Definitive treatment of TRAS involves angioplasty or surgical revision if percutaneous interventions fail.

Peritonitis or abdominal sources of sepsis in a liver transplant recipient should prompt an investigation into biliary duct complications, such as biliary leakage, stasis due to stenosis of the biliary duct, and cholangitis. Biliary leakage can be evaluated with a cholangiogram or endoscopic retrograde cholangiogram, which allows for simultaneous intervention. Anastomotic stenosis usually occurs within the first year posttransplantation. Nonanastomotic stenosis can be caused by hepatic artery thrombosis or recurrence of an underlying disease such as primary sclerosing cholangitis and can manifest later. Treatments include balloon dilation and stent placement. Although becoming less frequent, coagulopathy with resultant hemorrhage, including post-op intra-abdominal hemorrhage, should also be considered in liver transplant recipients.

Lung recipients with respiratory failure must be evaluated for both infectious complications, including bacterial, viral, and fungal pneumonia, as well as immune-mediated allograft dysfunction. This workup often requires bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. It is important to evaluate for and treat infections, given that the therapy for acute immune-mediated graft dysfunction (including acute cellular rejection and antibody-mediated rejection) generally involves high-dose immunosuppression, such as methylprednisolone 500 to 1,000 mg for several days, antithymocyte

globulin, and/or antibody-directed therapies such as plasma exchange, rituximab, and bortezomib.

Heart transplant recipients with evidence of graft dysfunction need to be evaluated for acute rejection, antibody-mediated rejection, and coronary artery vasculopathy. This evaluation often starts with noninvasive testing such as echocardiography, but often endomyocardial biopsy is necessary to fully evaluate the patient.

Lastly, in both transplant recipients and potential candidates, blood transfusion may increase the risk of allosensitization, and blood products should be used judiciously. In the United States, most blood products undergo leukoreduction. However, there are a minority of independent blood centers that have not implemented universal leukoreduction, and leukoreduced blood should be requested for SOT recipients. In addition, CMV seronegative blood products are available in some institutions for recipients who have received organs from CMV seronegative donors, although its advantage in preventing CMV transmission over leukoreduced blood is unclear. Irradiated blood products are generally not necessary as transfusion-associated graft-versus-host disease (GVHD) in SOT recipients is exceedingly rare. However, the use of anti-CD52 antibody alemtuzumab as an induction agent is an exception, and the use of irradiated blood products until the recovery of lymphopenia is recommended.

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SECTION XVI PREGNANCY

71 Maternal-Fetal Critical Care

Rebecca Rimsza and Michael Dombrowski

Although less than 1% of pregnant patients will require admission to the intensive care unit (ICU), the overall acuity of this patient population remains high. The Due incidence of pregnancy-related ICU admission is anticipated to increase over time to the increasing maternal age and prevalence of comorbid medical conditions. Over half of the ICU admissions in pregnancy are directly related to obstetric conditions such as hypertensive disorders from eclampsia/severe preeclampsia and hemorrhage. However, a pregnant patient may require critical care for almost any reason, and management must consider the health of both the mother and the fetus. To provide optimal care for a pregnant patient who is critically ill, multidisciplinary team management is essential. To fully understand the care needs of this vulnerable patient population, it is important to understand the basic physiologic adaptations that occur in the mother in response to the demands of pregnancy (Table 71.1), as well as the importance of gestational age of the fetus.

TABLE 71.1 Physiologic Changes of Pregnancy

Cardiovascular	
BP	Decreased (reaches a nadir in the second trimester)
Heart rate	Increased (17%)
Cardiac output	Increased (40%)
Stroke volume	Increased (25%)

Cardiovascular	
Systemic vascular resistance	Decreased (20%)
Hematologic	
Blood volume	Increased (40%-50%)
Coagulation factors	Increase in fibrinogen, vWF, clotting factors II, VII, VIII, IX, and X and protein C resistance. Decrease in protein S
Red blood cell mass	Increased
White blood cell count	Increased
Hemoglobin	Decreased
Platelets	Decreased (secondary to hemodilution)
Renal	
Glomerular filtration rate	Increased (50%)
Renal plasma flow	Increased (50%-75%)
BUN and creatinine	Decreased
Urinary protein excretion	Increased
Pulmonary	
Tidal volume	Increased (40%)

Cardiovascular	
Respiratory rate	Little to no change
Minute ventilation	Increased (40%)
Vital capacity	Unchanged
FEV_1	Unchanged
Residual volume	Decreased (20%)—secondary to elevated diaphragm
FRC	Decreased (20%)—secondary to elevated diaphragm
Inspiratory capacity	Increased (5%-10%)—secondary to decreased FRC

BP, blood pressure; BUN, blood urea nitrogen; FEV, forced expiratory volume; FRC, functional residual capacity; vWF, von Willebrand factor.

Maternal mortality in the United States has been steadily increasing and is 3 times higher than the mortality rate in other high-income countries. Unfortunately, patients of the Black population bear the majority of this burden, with significantly higher rates of morality at 42 per 100,000 versus 13 per 100,000 for their White peers. Women of color suffer from implicit bias, systemic racism, and socioeconomic disadvantages, resulting in significant barriers to prenatal care, delays in diagnosis, and ultimately, elevated morbidity and mortality rates. Efforts toward preventing maternal mortality are ongoing, but high-quality critical care is imperative to help improve outcomes.

Providing care for a pregnant patient who is critically ill can be anxiety-provoking, even for experienced intensive care providers. Two broad concepts can help alleviate some of this stress. The first is considering “what would you do if the patient were not pregnant.” As discussed in this chapter, critical care remains largely unchanged by pregnancy status, with only minor changes. The second is “the

best way to take care of the fetus is to take care of the patient." Providers can be blinded by concern for the fetal unit, and in an attempt to optimize fetal well-being, provide substandard maternal care, which is likely to worsen fetal outcome.

Respiratory Changes of Pregnancy

The normal physiologic changes of pregnancy increase oxygen delivery to both the placenta and the fetus. Fetal oxygenation is dependent on the maternal oxygen status. It is important to note that pregnancy is a chronically compensated state of mild respiratory alkalosis, with maternal pH ranging from 7.40 to 7.47. This respiratory alkalosis is secondary to an increase in minute ventilation, which leads to a decrease in mean P_{CO_2} to approximately 30 mm Hg. This is compensated by an increased renal excretion of bicarbonate (normal value in pregnancy: 18-22 mEq/L).

Pregnancy increases oxygen consumption by 15% to 20%. Pregnancy-associated anemia results in lower hemoglobin concentration and arterial oxygen content; however, an increase in cardiac output during this time optimizes oxygen delivery. Maintaining cardiac output is therefore pivotal to oxygen delivery in pregnancy. Bearing in mind the physiologic changes in ventilation during pregnancy and the fetal oxygen dissociation curve, tighter parameters for oxygenation are often suggested to maintain maternal and fetal well-being. If feasible, expert opinion is to maintain maternal Sp_{O_2} greater than or equal to 95% to sustain adequate oxygen perfusion to the fetus. However, if achieving this goal carries a risk (eg, excessive F_{IO_2}, high ventilator pressures), then lower targets can be used if fetal monitoring remains nonworrisome. The same respiratory support devices used in nonpregnant patients may be used in pregnant patients. Indications for intubation are similar to the general population. As mentioned earlier, P_{CO_2} above 35 mm Hg indicates CO_2 retention. If allowed by fetal status, then permissive hypercapnia is utilized as in a

nonpregnant patient. Patients who are pregnant should be considered to have difficult airways secondary to tissue laxity, edema, reduced esophageal sphincter tone, and diminished reserve.

Prone positioning is safe in pregnancy. Proper positioning includes liberal use of foam/pillow support to minimize abdominal compression. Videos are available online to guide the prone positioning of pregnant patients.

Cardiovascular Changes in Pregnancy

Pregnancy represents a significant stress on the cardiovascular system. Blood volume increases by 50%, leading to an imbalance in plasma volume and red blood cell mass, resulting in the development of physiologic anemia. Systemic vascular resistance decreases to compensate for the increased volume, while heart rate increases. Blood volume peaks around 35 weeks of gestation, representing a common time for cardiac decompensation.

Hemodynamics of Delivery

Uterine blood flow reaches 500 to 1,000 mL/min at full term. During delivery, significant blood loss can occur, with losses up to 1,000 mL considered normal. Massive postpartum hemorrhage due to uterine atony can result in blood loss of 5 to 10 L or more. Following delivery, maternal blood volume will receive an “autotransfusion” when blood flow to the uterus deceases and is shunted back to systemic circulation, making the first 72 hours following delivery a high-risk time for fluid overload. Most patients tolerate this well, but patients at high risk for decompensation in the setting of fluid overload (aortic stenosis, mitral stenosis, single ventricle physiology, etc) should be monitored very closely.

Importance of Gestational Age

The gestational age of the fetus or embryo can have a dramatic impact on the management of the pregnant patient who is critically ill. While pregnancy is commonly divided into trimesters or months, obstetricians prefer a more fine-grained description of gestational age, because even a one week change can affect management decisions. Broadly, pregnancy can be categorized as “previable” or “viable,” reflecting the possibility of neonatal survival following delivery. This involves a combination of factors including gestational age, estimated fetal weight, and local standards. Most commonly, the lower limit of viability is 22 to 24 weeks. Incidence of survival varies during the periviable period from as low as 13% at 22 weeks to 68% at 25 weeks (Figure 71.1), with neonates born at 26 weeks or later generally having good outcomes. Prior to viability, delivery for fetal benefit is not possible and should only be carried out for maternal benefit. Fetal surveillance in this case is limited to periodic fetal heartbeat assessment via handheld Doppler or ultrasound.

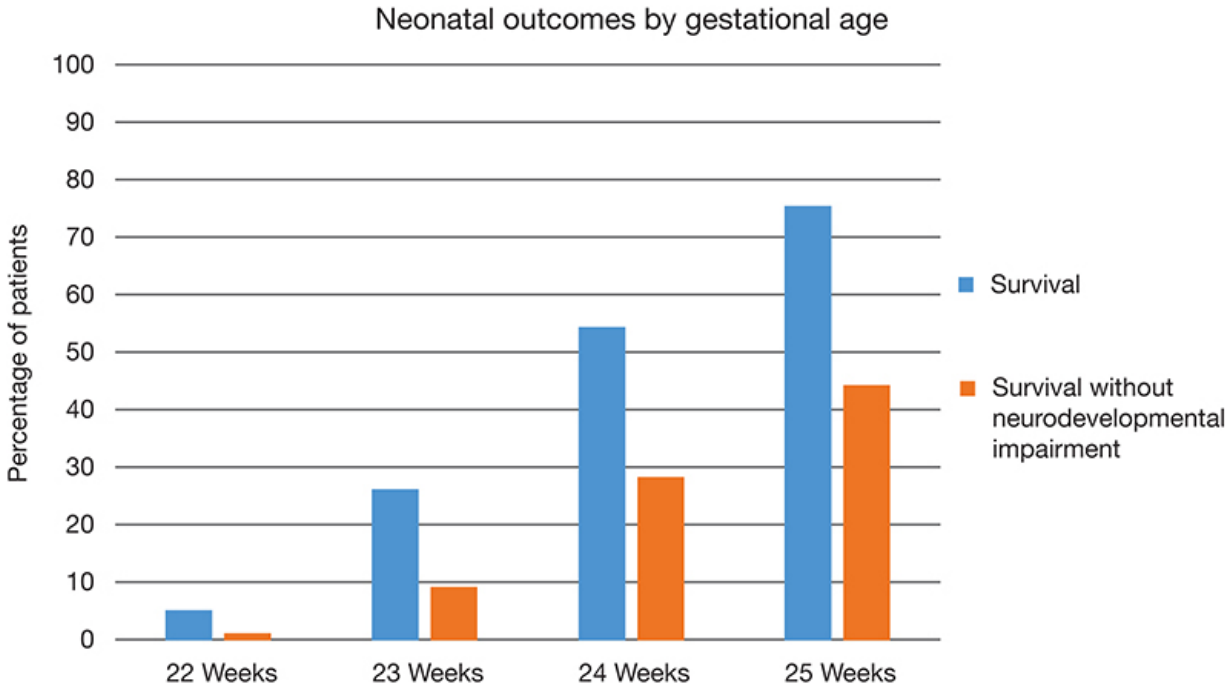


FIGURE 71.1 **Survival for one data group and survival without neurodevelopmental impairment in the other.** X axis,

gestational age; Y axis, number of patients.

Once viability is achieved, management becomes more complicated. Fetal heart rate monitoring via electronic heart rate monitoring on the abdomen can be performed, but this decision involves shared decision-making with the patient and/or their family following multidisciplinary counseling including obstetricians, neonatologists, and critical care teams. The need for emergent delivery in the setting of critical illness can worsen maternal prognosis and should be carefully considered. Decreasing cardiovascular and respiratory needs following delivery can lead to improvement; however, these must be weighed against the risks of delivery and rapid physiologic changes of the postpartum period. Critical illness does not mandate cesarean delivery; however, there is a lack of high-quality data to guide the route or timing of delivery in the setting of critical illness, and this decision must be individualized.

Pregnancy-Specific Disorders

INTRODUCTION

Pregnancy-specific causes of critical illness include amniotic fluid embolism (AFE), acute fatty liver of pregnancy, obstetric hemorrhage, peripartum cardiomyopathy (PPCM), and preeclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. For all pregnancy-related causes of critical illness, supportive care is the mainstay of treatment, and no specific treatment (other than delivery) is available. Preeclampsia significantly drives maternal morbidity and is a common cause for ICU admission. Due to the complexity associated with this condition, Chapter 72, Preeclampsia and Eclampsia, is dedicated to the diagnosis and management of complications.

Amniotic Fluid Embolism

With an incidence of about 1 in 15,000 deliveries, AFE is a rare but devastating obstetric disorder—the maternal mortality rate can be as high as 60%. The pathophysiology of AFE is poorly understood. It appears to be due to an abnormal maternal immune response to fetal antigens, which is why AFE is sometimes referred to as an anaphylactoid syndrome of pregnancy. Classically, a pregnant woman in labor, or 30 minutes postpartum, will present with a sudden onset of acute hypoxia, acute hypotension with/without cardiac arrest, followed by fetal hypoxia (if patient is still pregnant), and coagulopathy. Unfortunately, for women who suffer from an AFE in its classic form, maternal death is the most common outcome.

When a patient experiences hypoxia, hypotension, coagulopathy, or cardiopulmonary arrest immediately following cesarean, vaginal delivery, or pregnancy termination, AFE must be suspected. Clinical variations of the syndrome exist, but a biphasic hemodynamic response is commonly seen with initial right ventricular failure and pulmonary hypertension due to vasoconstriction followed by left ventricular failure often complicated by diffuse coagulopathy. The initial treatment for AFE is supportive care with immediate, high-quality cardiopulmonary resuscitation (CPR) as necessary and close monitoring of hemodynamic parameters including echocardiography. If patients become hypotensive, they may require volume expansion to optimize preload, as well as inotropic support or pulmonary vasodilators. Given the propensity for the development of acute heart failure and cardiogenic pulmonary edema in AFE, care should be taken to avoid excessive fluid resuscitation. When coagulopathy is suspected, massive transfusion protocol should be initiated to facilitate blood product support. Novel treatments for AFE, including extracorporeal membrane oxygenation (ECMO), exchange transfusion, and cardiopulmonary bypass or assist devices have shown benefit in case reports.

In antepartum cases of AFE, fetal status must be followed closely. Initially, every attempt should be made to hemodynamically stabilize the mother, as this will serve to resuscitate the fetus, and cesarean section on an unstable patient may contribute to mortality in the setting of AFE. Once the patient is stabilized, delivery should be

performed to improve resuscitation of the mother and neonatal survival.

Acute Fatty Liver

Acute fatty liver of pregnancy represents another rare but potentially fatal complication of pregnancy. It is characterized by microvesicular fatty infiltration of hepatocytes, resulting in acute and often profound liver failure. Diagnosis is largely clinical, but laboratory indices, including hypoglycemia (often <60 mg/dL), hyperammonemia, elevated aminotransferases, thrombocytopenia, hypofibrinogenemia, and disseminated intravascular coagulation, can be helpful. Liver biopsy is gold standard for diagnosis, but it is rarely needed, as prompt delivery most commonly results in a rapid return of liver function. Rarely, patients do not improve and liver transplantation is required.

Obstetric Hemorrhage

Obstetric hemorrhage is a relatively common cause of pregnancy-related morbidity. The placenta and uterus are highly vascular organs that can lead to high-volume hemorrhage within a matter of minutes. Hemorrhage can be broadly categorized into antepartum (predelivery), intrapartum (during delivery), and postpartum (following delivery).

When considering antepartum hemorrhage, common causes include placental abruption or placental previa. Placental abruption occurs when the placenta peels away from the uterine walls, allowing for unopposed bleeding into the uterus. Sudden acute onset of abdominal pain associated with vaginal bleeding is the most common presentation. This can be accompanied by fetal distress, and emergent cesarean delivery often results. The bleeding from the placenta can also be “concealed” without vaginal bleeding. In these cases, high-volume bleeding into the uterus can cause an

unanticipated coagulopathy and result in even higher levels of blood loss.

Placenta previa occurs when the placenta implants over the cervix. As patient's cervix shortens and dilates in preparation for delivery, the placental vessels stretch and bleed. The classic presentation is painless vaginal bleeding. Urgent cesarean delivery for control of bleeding is imperative.

Placenta accreta spectrum is a potentially life-threatening complication of the placenta that grows into, and, sometime, through the uterine wall. Standard management is cesarean delivery followed by hysterectomy. However, the hysterectomy is complicated by enlarged uterine vessels and prior abdominal surgeries, making hemorrhage and inadvertent injury to surrounding structures (bladder or ureters) common. Preparation for a cesarean hysterectomy includes anticipation of high-volume blood product resuscitation and expert gynecologic surgeons. Some centers include preoperative interventional radiology consultation for consideration of uterine artery embolization following delivery and prophylactic tranexamic acid. A more advanced form of placenta accreta involves the placenta growing through the uterus and into surrounding structures, such as bladder, bowel, or vasculature, including iliac vessels. An unrecognized placenta accreta with delivery in a rural or low-risk center is associated with a high rate of mortality.

Postpartum hemorrhage following delivery is usually due to uterine atony. Following the expulsion of the placenta, the uterus contracts to restrict blood flow and bleeding ceases. However, if the uterus does not contract, hemorrhage occurs. Multiple medications are available for management of uterine atony, including carboprost, methylergonovine, misoprostol, and oxytocin. Mechanical methods for hemorrhage include intrauterine balloon tamponade (eg, Bakri or Ebb balloons) or an intrauterine vacuum device to aid uterine contraction (Jada device). If other methods fail, transition to the operating room for laparotomy or interventional radiology for embolization is recommended.

Principles of hemorrhage management include identification of underlying cause of bleeding, rapid management, and massive

transfusion with close assessment and management coagulopathy. Maternal fibrinogen levels predict the severity of hemorrhage, and emerging data support the use of a “fibrinogen first” strategy for treating coagulopathy with fibrinogen concentrate or cryoprecipitate. Obstetric patients are often young and healthy and may tolerate significant blood loss without traditional signs of volume depletion; therefore, frequent bloodwork and close assessment of blood loss are needed.

Peripartum Cardiomyopathy

Incidence of PPCM is approximately 1 in 2,000 patients, making it a common indication for critical care. Patients present with new-onset heart failure without a known cause. Diagnosis is via echocardiogram with ejection fraction less than or equal to 45% with or without ventricular dilation. PPCM most commonly occurs within 1 month of delivery but may also occur prior to delivery or within 1 year postpartum. Presentation includes signs or symptoms of heart failure, including shortness of breath, fatigue, edema, and tachypnea.

Treatment includes multidisciplinary management between obstetrics, cardiology, and critical care. Principles of acute heart failure management are applied, including diuresis and beta-blockade, with antihypertensive therapy as needed. Following delivery, the addition of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) may be added. Enoxaparin is commonly added for patients with severely decreased left ventricular ejection fraction (LVEF; <30%) due to intraventricular clot risk. Recent experimental treatments have focused on bromocriptine to potentially improve recovery; however, usage should be limited to Institutional Review Board (IRB)–approved research protocols.

Delivery in the setting of acute heart failure presents a significant challenge. Coordination of care involving a multidisciplinary team, including obstetrics, cardiology, maternal-fetal medicine,

anesthesiology, and neonatology, is needed. Attempts to stabilize the patient to avoid delivery in the acute period are reasonable. Invasive hemodynamic monitoring may be beneficial to assess for rapid fluid shifts. If LVEF is particularly poor, the ECMO team should be included in case urgent cannulation is needed postpartum.

The long-term prognosis of PPCM varies from complete recovery to permanent dysfunction or even deterioration requiring heart transplant.

Hypercoagulability/Thromboembolism

Pregnancy represents a hypercoagulable state, as venous thromboembolism (VTE) risk being 4 to 50 times higher in pregnant women. The risk of VTE peaks in the postpartum periods, within the first 6 weeks following delivery. Compounding additional risk factors such as obesity, recent surgery (cesarean delivery), diabetes, or other commodities make pulmonary embolism one of the leading causes of maternal mortality.

Any pregnant patient presenting with tachycardia, shortness of breath, or chest pain should be evaluated for pulmonary embolism. Both ventilation-perfusion ($\dot{V}/\dot{Q}$) scans and CT scans are acceptable imaging studies. Treatment with anticoagulation and/or thrombectomy is reasonable, and patients should be managed similar to the nonpregnant patients. Pregnant patients in the ICU setting should receive prophylactic anticoagulation.

Extracorporeal Membrane Oxygenation in Pregnancy

Pregnancy is not a contraindication to ECMO. A recent review article suggests that pregnant patients have a lower incidence of in-hospital death and bleeding complications, likely due to their young and otherwise healthy population. In patients at a previable gestational

age, ECMO should be used as indicated, following the same protocols as for nonpregnant patients. Once viability has been reached, ECMO cannulation can be considered with the goal of achieving recovery and eventual decannulation, allowing for continued pregnancy. For patients in late pregnancy, delivery immediately before or after ECMO cannulation can be considered following a multidisciplinary consensus. Delivery for patients on ECMO carries a high risk of hemorrhage, both during the delivery (via cesarean) and postpartum. Limited data suggest lower maternal risk with cannulation and continued pregnancy than cannulation after delivery. Coordination between maternal-fetal medicine, cardiothoracic surgery, the critical care team, and neonatology is necessary to ensure adequate preparation and safe care during ECMO.

Cardiopulmonary Resuscitation/Resuscitative Hysterotomy

Cardiac arrest during pregnancy is most commonly due to respiratory insufficiency or hemorrhage/hypotension, and initial rhythms are usually nonshockable. Management follows advanced cardiovascular life support (ACLS) guidelines with minor modifications for patients at or beyond 20 weeks of gestation (identifiable by uterine fundus at or above the umbilicus). At this gestational age, the uterus is above the bifurcation of the aorta and can cause aortocaval compression. Therefore, the uterus should be manually displaced to the maternal left to facilitate return of blood flow. A provider positioned on the patient's right can use one hand to push the uterus to the left, or a provider on the maternal left can use two hands to pull the uterus. Tilting the patient using a wedge is not recommended as it may reduce CPR efficacy.

While performing CPR with uterine displacement, the obstetric team should be contacted for consideration of a resuscitative hysterotomy (previously called perimortem cesarean section).

Prompt fetal delivery has been shown to improve maternal outcomes and, in cases of a viable fetus, may also improve neonatal survival. This should be accomplished by 5 minutes of the start of maternal cardiac arrest if return of spontaneous circulation is not achieved prior.

Intravenous lines should be placed above the diaphragm in this scenario, and for reasons addressed earlier, airway management should be attempted by the most experienced provider available. If the patient is receiving a magnesium infusion, this should be stopped, and calcium should be administered in cases of magnesium toxicity.

Medication Safety in Pregnancy

Medication safety is a common concern for intensivists caring for pregnant or lactating patients. In general, for patients who have passed the critical period of organogenesis (>10 weeks), there are few medications that are absolutely contraindicated. The pregnancy category system (A, B, C, D, X) was widely known, but these categories were removed from drug labeling by the US Food and Drug Administration (FDA) rule in 2014, so the relevance of a drug's category should be de-emphasized. For specific medication questions, consultation with the obstetric team is recommended. Resources such as Micromedex and MotherToBaby.com can also be used for additional support.

Analgesics and sedatives should not be withheld due to pregnancy. Opioid medications, including oxycodone, morphine, and fentanyl, can be used with the basic principle of administering the smallest amount for the shortest amount of time. These medications are known to cross the placenta but are not teratogenic. Sedatives, including propofol, dexmedetomidine, ketamine, and benzodiazepines, can be used in pregnancy. If maternal dosing is continued through delivery, the neonatal team should be made aware in case of neonatal respiratory depression. Other commonly used medications, including vasopressors, antibiotics, steroids, and

paralytics, are broadly safe in pregnancy and lactation. Heparin and enoxaparin do not cross the placenta and are the anticoagulants of choice.

Imaging

Radiation exposure from diagnostic or interventional studies is another area of common concern for intensivists. Plain film radiographs and CT imaging, other than the abdomen/pelvis, represent minimal exposure. If feasible, nonionizing imaging studies such as ultrasound or MRI should be used for abdominal and pelvic imaging. However, if needed, ionizing abdominal and pelvic imaging can be safely used. Oral and intravenous contrast agents have not been shown to be harmful and can be used if indicated. Intravenous gadolinium may carry fetal risk and should only be administered if its use significantly improves diagnostic performance and will yield clinically actionable results.

Blood Transfusion in Patients of Childbearing Potential

Routine transfusion practices are not influenced by pregnancy status. Traditionally, patients of childbearing potential who require massive transfusion have been limited to Rh-negative units until their Rh status is identified, which often precludes use of whole blood for resuscitation. The concern comes from the potential to develop antibodies against Rh+ blood, which could, in a future pregnancy, cause fetal hemolysis. Clinical experience and modeling suggest that the risk of adverse fetal outcome in a subsequent pregnancy is much lower than had been expected. Modern obstetric care allows for intrauterine transfusion though that procedure is not without risk or cost. In light of the rarity of adverse outcomes and increasing strength of evidence for whole blood, an increasing number of

trauma centers are using low-titer O+ whole blood for all patients, regardless of future childbearing potential.

Practical Considerations for the Pregnant Patient

Some general principles to consider for ICU care: Patients who at or beyond 20 weeks of pregnancy should be positioned with a left lateral tilt to avoid aortocaval compression, most commonly accomplished with a “bump.” For patients at or beyond 20 weeks gestation in the ICU, there should be ready available instruments to accomplish emergent cesarean delivery. If the pregnancy has past the point of viability, the neonatology team should be informed of the patient’s status and location, with consideration given to colocation of neonatal resuscitation equipment. Any significant changes in patient’s status should prompt notification of the obstetric team. Fetal monitoring can be used to assess fetal tolerance to maternal physiologic state (eg, blood pressure, oxygenation, ventilation). Monitoring devoid of concerning features can be used to support lower maternal oxygenation targets or permissive hypercapnia, as mentioned earlier. Care must be taken in the interpretation of fetal monitoring, as interventions, such as sedation, can blunt reassuring features on monitoring (but not concerning features such as decelerations), so we use the absence of concerning features as sufficient reassurance of fetal status. Signs of fetal compromise should not prompt reflexive delivery of the pregnant patient who is critically ill; rather, they should prompt a search for correctible causes.

Lactation is an important consideration for postpartum patients. In the setting of critical illness, milk production may be minimal; however, if desired, the lactation support team should be involved, and pumping equipment should be brought to the bedside.

72 Preeclampsia and Eclampsia

Molly J. Stout and Jessica M. Despotovic

Preeclampsia is a hypertensive disorder of pregnancy characterized by elevated blood pressure and evidence of end-organ dysfunction that typically occurs after 20 weeks of gestation. It can also occur in the early postpartum period. The classic definition of preeclampsia included the presence of hypertension and proteinuria. However, preeclampsia can be diagnosed in the absence of proteinuria if there is evidence of end-organ involvement, such as thrombocytopenia, renal insufficiency, impaired liver function, neurologic or visual disturbances, or pulmonary edema. Preeclampsia complicates approximately 12% to 22% of all pregnancies, and is it directly responsible for 17% of maternal deaths in the United States. Risk factors for preeclampsia include a history of preeclampsia in a prior pregnancy, nulliparity, age older than 35 years, multifetal gestations, in vitro fertilization, obesity, underlying chronic hypertension or chronic kidney disease, diabetes, thrombophilia, vascular and connective tissue disorders, and obstructive sleep apnea.

The exact pathophysiologic mechanism for preeclampsia is unknown, but it is likely related to the dysregulation of placental factors such as regulators of angiogenesis, growth factors, cytokines, and regulators of vascular tone. This dysregulation ultimately leads to poor perfusion of various organs, including the central nervous system (CNS), kidneys, and the fetoplacental unit. It is notable that the underlying physiology of preeclampsia involves placental trophoblastic tissue and can occur in the absence of a fetus, as seen in women with a hydatidiform mole.

Diagnosis

Preeclampsia can manifest with a wide range of disease severity, from asymptomatic hypertension to life-threatening neurologic, renal, or coagulopathic abnormalities. Hypertension is defined as blood pressure equal to or greater than 140 systolic or equal to or greater than 90 diastolic on two occasions at least 4 hours apart in a woman with previously normal blood pressure. Severely elevated blood pressure equal to or greater than 160 systolic or equal to or greater than 110 diastolic, confirmed within a few minutes (to expedite treatment), is also diagnostic. Proteinuria is defined as urinary excretion of 300 mg of protein in a 24-hour urine collection; alternatively, a protein/creatinine (mg/dL) ratio of at least 0.3 is an acceptable equivalent.

Preeclampsia is a progressive disease, and women must be monitored for the development of severe features (listed in Table 72.1), which, when present, increase the risk of morbidity and mortality. Severe, life-threatening complications are listed in Table 72.2.

TABLE 72.1 Severe Features of Preeclampsia

Hypertension	Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≤110 mm Hg (can be confirmed within a short interval to expedite treatment)
CNS	Neurologic or visual disturbances, including headache
Thrombocytopenia	Platelet count ≤100,000/mcL
Renal	Acute kidney insufficiency (serum creatinine concentration >1.1 mg/dL or doubling of serum creatinine)
Hepatic	Elevation in transaminases (to twice normal concentration), epigastric or right upper quadrant pain
Pulmonary	Pulmonary edema

CNS, central nervous system.

TABLE 72.2 End-Stage Complications in Patients With Preeclampsia/Eclampsia

System	Complications
CNS	Seizures, cerebrovascular hemorrhage, temporary cortical blindness
Cardiopulmonary	Critical hypertension, heart failure, cardiopulmonary arrest, pulmonary edema
Renal	Acute renal failure
Hepatic	Subcapsular hematoma, hepatic rupture with hemorrhage
Hematologic	Disseminated intravascular coagulation, hemolysis
Fetal	Fetal demise, placental abruption, intrauterine growth restriction, preterm delivery

CNS, central nervous system.

The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) is a life-threatening variant of severe preeclampsia. Women with HELLP syndrome may present with vague epigastric discomfort or mild nausea and vomiting. Notably, HELLP can be found in patients with minimal or absent hypertension and proteinuria. The laboratory findings in HELLP syndrome overlap with other life-threatening complications of pregnancy such as acute fatty liver of pregnancy and thrombotic thrombocytopenic purpura, which should be considered in the differential diagnosis. The main differential diagnosis of preeclampsia/eclampsia/HELLP syndrome is presented in Table 72.3, and several helpful laboratory tests are presented in Table 72.4. HELLP syndrome is associated with an increased risk for both maternal and fetal adverse outcomes, including placental abruption, renal failure, recurrent preeclampsia, preterm delivery, and maternal or fetal death.

TABLE 72.3 Key Differential Diagnosis of Severe Preeclampsia/Eclampsia/HELLP

1. CNS
   a. Seizure disorder
   b. Hypertensive encephalopathy
   c. Cerebrovascular
      i. Intraventricular-intracerebral hemorrhage
      ii. Arterial embolism or thrombosis
      iii. Hypoxic ischemic encephalopathy
      iv. Angioma, atrioventricular malformation, or aneurysm
   d. Reversible posterior leukoencephalopathy syndrome
   e. Tumors
   f. Cerebral vasculitis
2. Thrombotic thrombocytopenic purpura
3. Acute fatty liver of pregnancy
4. Metabolic disease
   a. Hypoglycemia
   b. Hyponatremia

CNS, central nervous system; HELLP, hemolysis, elevated liver enzymes, and low platelets.

TABLE 72.4 Imitators of Preeclampsia/HELLP: Laboratory Findings

Laboratory Finding	Normal Pregnancy	Preeclampsia/HELLP	TTP	AFLP
Hematocrit	↓ 4%-7%	↑ with hemoconcentration ↓ with hemolysis	↓	↔
Platelet count	Slight ↓, but remains >150,000 mcL	↓	↓	↔ to slight ↓

Laboratory Finding	Normal Pregnancy	Preeclampsia/HELLP	TTP	AFLP
Fibrinogen	↑ (nl >300 mg/dL)	↔ or may ↓ with thrombocytopenia, DIC	↔	↓
PT and PTT	↔	↔ except in DIC	↔	↑
Serum creatinine	↓	↑	↑	↑
Serum uric acid	↓ 33%	↑	↑	↑
Urine protein	↑ but remains <300 mg/d	↑ >300 mg/d		
Protein/creatinine ratio <0.19[a]	Protein/creatinine ratio >0.19[a]	↔ to ↑	↔	
Hepatic transaminases	↔	↑	↔ to ↑	↑
WBC	Slight ↑	↔	↑	↑
LDH	↔	↑	↑	↑
Glucose	↔	↔	↔	↓
Ammonia	↔	↔	↔	↓
Bilirubin	↔	↑	↑	↑ (>5 mg/dL)

AFLP, acute fatty liver of pregnancy; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, and low platelets; LDH, lactate dehydrogenase; nl, normal; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura; WBC, white blood cell.

[a]Shown to correlate strongly with 24-hour urine protein quantity.

Modified with permission from Sibai BM. Imitators of severe preeclampsia/eclampsia. *Clin Perinatol*. 2004;31:835-852.

Eclampsia is defined as preeclampsia with generalized tonic-clonic seizures and/or coma. Approximately 50% of all cases of eclampsia are diagnosed during the antepartum period, 20% present with an intrapartum event, and the remaining 30% are diagnosed during the postpartum period. Although most postpartum seizures occur in the first 48 hours, cases have been reported as late as 3 weeks after delivery. Notably, nearly 15% of women with eclampsia initially present without hypertension, and another 15% may lack proteinuria. Furthermore, the severity of hypertension and the amount of proteinuria in a patient with preeclampsia are poor predictors of progression to eclampsia.

Women with underlying chronic hypertension or proteinuria present a diagnostic challenge. Worsening hypertension relative to measurements early in pregnancy or hypertension that becomes refractory to antihypertensive medications can be used as diagnostic clues. In addition, worsening proteinuria from a baseline 24-hour urine protein obtained early in pregnancy can also be used. Certainly, any development of end-organ damage or HELLP syndrome suggests superimposed preeclampsia.

Pathophysiology by Organ System

VASCULAR

Hemoconcentration and hypertension are the main vascular changes in preeclampsia. Women with preeclampsia may not develop the normal hypervolemia of pregnancy. Vascular reactivity, mediated by alterations in prostaglandins, prostacyclin, nitric oxide, and endothelin, cause intense vasospasm and intravascular contraction. Alterations in plasma oncotic pressure and endothelial leak can cause third spacing of fluid manifested as edema. Careful attention to fluid status is required, as aggressive resuscitation with crystalloids or colloids can often cause pulmonary edema.

HEMATOLOGIC

Hematocrit may be increased secondary to hemoconcentration. In the context of HELLP syndrome, hematocrit may be low due to hemolysis. Thrombocytopenia also characterizes HELLP syndrome.

HEPATIC

Elevation of transaminases to at least twice normal concentration is a severe feature of preeclampsia. Hepatic hemorrhage with hepatic capsule irritation may cause right upper quadrant pain. Hepatic rupture is rare but is associated with catastrophic outcome.

CENTRAL NERVOUS SYSTEM

Eclampsia and intracranial hemorrhage are associated with increased maternal mortality. Temporary blindness, headache, blurred vision, scotomata, and hyperreflexia are also signs and symptoms of CNS and are severe features of preeclampsia.

RENAL

Normal pregnancy physiology involves an increased glomerular filtration rate and renal blood flow resulting in decreased serum creatinine (typically ≤0.8 mg/dL). Vasospasm in preeclampsia causes a reversal of this normal physiologic change, and oliguria and increased serum creatinine may occur. Renal dysfunction is typically defined as a serum creatinine more than 1.1 mg/dL or a doubling of baseline serum creatinine in the absence of other renal disease.

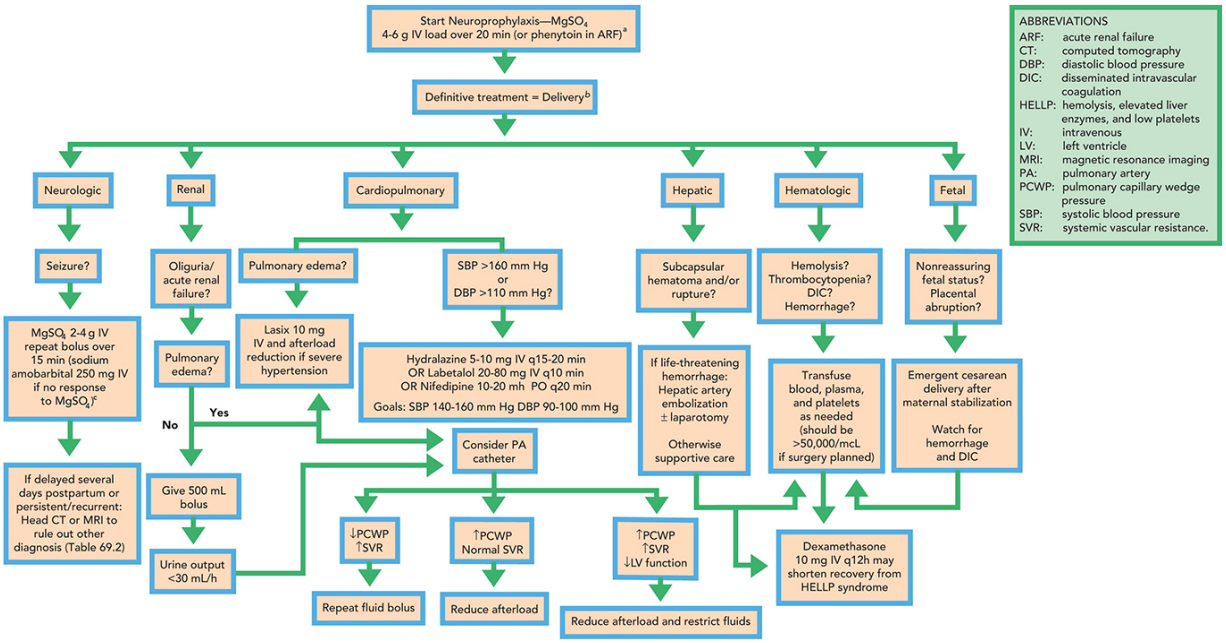
FETAL

Intrauterine growth restriction, oligohydramnios, and placental infarctions may be seen as manifestations of preeclampsia; however, they are no longer considered as diagnostic criteria.

Treatment

The definitive treatment of preeclampsia with severe features, eclampsia, and HELLP syndrome is delivery. The decision to proceed with delivery must balance maternal and fetal risks. Close attention should be initially paid to the medical stability of the mother, with consideration of specific target organs (Algorithm 72.1). Magnesium sulfate is the preferred antiseizure drug in the setting of preeclampsia/eclampsia. It is provided as an initial intravenous load of 4 to 6 g over 20 minutes, followed by continuous infusion of 2 g/h. During seizures, the patient's airway should be protected and adequate oxygenation is ensured. If seizures recur while the patient is receiving magnesium, a repeat (4 g) bolus of magnesium may be given. Other alternatives include intravenous administration of amobarbital or benzodiazepines (lorazepam or diazepam). Because magnesium undergoes renal clearance, frequent physical examinations should be performed to screen for magnesium toxicity, including arousability/neurologic status and deep tendon reflexes. Serum magnesium levels can be assessed in any woman with evidence of impaired renal function and the dose adjusted as needed to sustain a blood level between 4 and 7 mEq/L (4.8-8.4 mg/dL, 2-4 mmol/L). Meticulous attention to pulmonary status and deep tendon reflexes on clinical examinations should be used in women on magnesium sulfate infusions to prevent magnesium intoxication, which, in the most severe form, can cause cardiorespiratory collapse. Phenytoin may be used in women with impaired renal function or compromised cardiopulmonary function. Seizure prophylaxis should continue for 24 hours after delivery and extended if the patient does not demonstrate evidence of improvement.

ALGORITHM 72.1 **Treatment Guidelines for Patients With Severe Preeclampsia/Eclampsia**


Start Neuroprophylaxis—MgSO4 4-6 g IV load over 20 min (or phenytoin in ARF)a
Definitive treatment = Deliveryb
Neurologic
Renal
Cardiopulmonary
Hepatic
Hematologic
Fetal
Seizure?
Oliguria/ acute renal failure?
Pulmonary edema?
SBP >160 mm Hg or DBP >110 mm Hg?
Subcapsular hematoma and/or rupture?
Hemolysis? Thrombocytopenia? DIC? Hemorrhage?
Nonreassuring fetal status? Placental abruption?
MgSO4 2-4 g IV repeat bolus over 15 min (sodium amobarbital 250 mg IV if no response to MgSO4)c
Pulmonary edema?
Lasix 10 mg IV and afterload reduction if severe hypertension
Hydralazine 5-10 mg IV q15-20 min OR Labetalol 20-80 mg IV q10 min OR Nifedipine 10-20 mh PO q20 min
Goals: SBP 140-160 mm Hg DBP 90-100 mm Hg
If life-threatening hemorrhage: Hepatic artery embolization ± laparotomy
Otherwise supportive care
Transfuse blood, plasma, and platelets as needed (should be >50,000/mcL if surgery planned)
Emergent cesarean delivery after maternal stabilization
Watch for hemorrhage and DIC
No
Yes
Consider PA catheter
If delayed several days postpartum or persistent/recurrent: Head CT or MRI to rule out other diagnosis (Table 69.2)
Give 500 mL bolus
Urine output <30 mL/h
↓PCWP ↑SVR
↑PCWP Normal SVR
↑PCWP ↑SVR ↓LV function
Repeat fluid bolus
Reduce afterload
Reduce afterload and restrict fluids
Dexamethasone 10 mg IV q12h may shorten recovery from HELLP syndrome
ABBREVIATIONS
ARF: acute renal failure
CT: computed tomography
DBP: diastolic blood pressure
DIC: disseminated intravascular coagulation
HELLP: hemolysis, elevated liver enzymes, and low platelets
IV: intravenous
LV: left ventricle
MRI: magnetic resonance imaging
PA: pulmonary artery
PCWP: pulmonary capillary wedge pressure
SBP: systolic blood pressure
SVR: systemic vascular resistance.

[a]The loading dose of magnesium is followed by $MgSO_4$ 2 g/h with adjustment for therapeutic magnesium levels (4-7 mEq/L, 4.8-8.4 mg/dL).
[b]See exception in the text for a very preterm fetus (<34 wk) in a stable preeclamptic patient.
[c]Consider lorazepam or diazepam IV with careful attention to respiratory depression.

Once maternal stabilization is accomplished, the well-being of the fetus should be assessed using heart rate monitoring and ultrasonography. Emergency cesarean delivery is may become necessary if the fetal status worsens. The priority of maternal stabilization is particularly important during periods of maternal seizures, which may be associated with impaired fetal oxygenation and non-reassuring fetal status. However, fetal status often improves with stabilization of maternal status.

The predominant cause of fetal morbidity and mortality is prematurity. Preeclampsia without severe features may be expectantly managed to minimize the risk of prematurity and allow administration of corticosteroids for fetal lung maturity. However, severe preeclampsia involving eclampsia, persistent hypertension despite medical therapy, persistent CNS symptoms, pulmonary edema, HELLP syndrome, coagulopathy, abruptio placenta, and acute kidney insufficiency require expedited delivery. There are circumstances when severe preeclampsia can be expectantly managed, but these patients should be followed by a multidisciplinary obstetric team. When preeclampsia with severe features presents in the postpartum period, magnesium sulfate may

still be used to prevent eclamptic seizures. Similarly, if preeclampsia is diagnosed in association with molar pregnancy, uterine evacuation and curettage are necessary procedures to remove retained placental fragments.

Unlike other hypertensive disorders, the course of preeclampsia/eclampsia is not influenced by antihypertensive therapy. Treatment with these medications is designed to prevent maternal stroke and congestive heart failure. Furthermore, the patient with preeclampsia is often edematous secondary to extravasation of fluid into the interstitial tissues in the setting of capillary leakiness and reduced oncotic pressure. This results in reduced intravascular volume, despite the increase in total whole-body water that characterizes the disease. Therefore, vasodilatation should be performed carefully, as it may contribute to diminished organ perfusion, which may also impact uteroplacental perfusion and jeopardize the undelivered fetus. The use of furosemide should be reserved for the treatment of pulmonary edema. Antihypertensive drugs, including hydralazine, calcium channel blockers, or labetalol, are generally administered for the treatment of diastolic blood pressure levels of greater than or equal to 110 mm Hg or systolic blood pressure levels greater than or equal to 160 mm Hg. There is no clear evidence that one of these antihypertensive agents is superior to the others for improving maternal and/or fetal outcomes. Although not routinely indicated, head imaging using computed tomography or magnetic resonance imaging of women with preeclampsia may reveal reversible posterior leukoencephalopathy. Conditions that may prompt providers to obtain CNS imaging studies in order to rule out cerebrovascular hemorrhage or other diseases, including lateralizing signs, prolonged unconsciousness, papilledema, seizures while on magnesium sulfate, delayed presentation greater than 48 hours after delivery, or an uncertain diagnosis of eclampsia with suspicion of alternative etiologies for neurologic abnormalities.

Most women with preeclampsia/eclampsia are expected to have a full recovery after delivery and removal of trophoblastic tissue. It is rare for patients to develop chronic renal failure or permanent

neurologic deficits following preeclampsia. The recovery phase is heralded by the onset of increased diuresis, which can be expected within 24 hours after delivery, but, in rare cases, can be delayed up to 1 week postpartum. Because of the high incidence of preeclampsia in pregnancy, the severe sequelae of the disease are among the most common indications for admission of a pregnant or postpartum patient to an intensive care unit. With thorough, prompt, and coordinated care by perinatal and critical care specialists, most patients will recover from preeclampsia/eclampsia without residual disease. However, women with hypertensive disease of pregnancy are at increased risk for cardiovascular morbidity and mortality throughout their lifespan. These women should have yearly assessment of blood pressure, lipids, blood glucose, and body mass index.

New evidence suggests a benefit from the use of aspirin for the prevention of preeclampsia in women with certain characteristics, as well as those with a history of preeclampsia in a prior pregnancy.

SUGGESTED READINGS

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Baxter JK, Weinstein L. HELLP syndrome: the state of the art. *Obstet Gynecol Surv*. 2004;59:838-845.

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Dekker G, Sibai B. Primary, secondary, and tertiary prevention of preeclampsia. *Lancet*. 2001;357:209-215.

SECTION XVII surgical problems

73 Trauma Care for the Intensive Care Unit

Jessica K. Staszak, Rami Al-Aref, and Douglas J. E. Schuerer

Care of a traumatically injured patient is a complex issue, given the multiple potential systems that can be affected. This chapter reviews the initial evaluation and treatment of trauma patients and then focuses on injuries that are most likely to cause early intensive care unit (ICU) death. In addition, we review the management of common traumatic injuries most likely to result in ICU admission. A trauma patient requiring critical care generally involves multiple specialties for comprehensive treatment of all injuries, including general surgery, neurosurgery, orthopedic surgery, facial surgery, hand surgery, and rehabilitation medicine. This team approach is essential to ensure positive outcomes in the acutely injured patient. Another consideration for decision-making in trauma care is that the trauma patient is often younger than the typical ICU population. Most young patients have a high potential for recovery despite being extremely ill initially. The brevity of this guide prohibits a thorough review of all traumatic injuries and, instead, focuses on the most life-threatening related to eventual ICU care.

Trauma Evaluation

The basic tenets of the initial resuscitation and management of the injured patient are described in the Advanced Trauma Life Support course. This course was designed to teach all physicians the basics of trauma care to better standardize and improve delivery of early interventions. While most trauma patients are initially evaluated in an emergency department, transfers and other reasons may lead to a

trauma patient who has not yet been evaluated being placed directly in the ICU.

PRIMARY SURVEY

The primary survey is commonly remembered as the ABCDEs of trauma. It is performed rapidly but completely and systematically to avoid missing injuries.

Airway

Assess for:

1. Obstruction, including foreign bodies, facial fractures, or bleeding. Begin measures to remove obstruction and establish airway.
2. Patency, which may be compromised because of diminished Glasgow Coma Scale (GCS) following brain injury, intoxication, or swelling.

Note: Patients who are verbal without hoarseness or stridor usually have a patent airway, but this does not rule out future airway compromise. Maneuvers to obtain a definitive airway should begin immediately upon recognition of airway compromise and before other lifesaving interventions.

Potential problems:

1. Swelling leading to delayed airway collapse
2. Inability to obtain airway in a paralyzed patient necessitating placement of a surgical airway
3. Unknown laryngeal or tracheal disruption
4. Persistent maxillofacial bleeding causing airway obstruction

Possible interventions:

1. Maintaining position of comfort or optimal flow of blood away from airway

2. Orotracheal or nasotracheal intubation (awake or with rapid sequence anesthesia) for patients with diminished mentation (GCS ≤8), severe head, neck or chest trauma, or oxygen desaturation
3. Cricothyroidotomy
    a. If possible, extend the neck and palpate the cricothyroid membrane
    b. Make a 2- to 3-cm skin incision vertically over the cricothyroid membrane
    c. Bluntly dissect down to cricothyroid membrane and incise it horizontally
    d. Place small bougie through incision and advance a 6F endotracheal tube over it into the airway

Breathing and Ventilation

Assess for:

1. Adequate chest wall excursion not limited by mental status, rib fractures, or pain
2. Loss of or diminished breath sounds on either side from pneumothorax, hemothorax, pulmonary contusion, or other lung pathology
3. Evidence of bruising or laceration to the chest
4. Deviated trachea from tension pneumothorax or neck hematoma

Potential problems:

1. Airway compromise and ventilation failure may be difficult to discern from one another
2. Massive pulmonary injuries may present falsely as airway-related injury with severe dyspnea
3. Airway placement may worsen some pulmonary issues because of positive pressure ventilation (ie, worsening pneumothorax)

4. Tension physiology may develop rapidly from either hemo- or pneumothorax

Possible interventions:

1. Check for lung slide on ultrasound or obtain chest x-ray to rapidly assess
2. Finger or tube thoracostomy for chest decompression. Needle decompression also an option, but is less reliable particularly in setting of hemothorax.
3. Mainstem the endotracheal tube down the bronchus contralateral to injury, over a bougie if necessary

Circulation With Hemorrhage Control

Assess for:

1. Blood volume and cardiac output
    a. Mental status deteriorates proportionately with increasing volume of blood loss and progression of hemorrhagic shock (see Table 73.1).
    b. Narrowed pulse pressure may be the first sign of hemorrhage.
    c. Both ashen gray skin and poor capillary refill imply poor circulation.
    d. Pulses are a marker of perfusion in the younger patient without vascular disease. Presence of a central pulse indicates systolic blood pressure of at least 70 to 80 mm Hg.
        - Full and regular pulses: Normal
        - Fast, thready, or diminished pulses: Poor flow to affected extremity versus global malperfusion
        - Irregular pulses: Possible blunt cardiac injury
    e. Four stages of hemorrhagic shock
2. Bleeding
    a. External blood loss is recognized readily and best stopped by direct pressure.

b. Occult bleeding from internal hemorrhage should be expected if patient has signs of shock.

c. Potential sources are:

i. Abdomen: Bruising, tenderness, or distension

ii. Chest: Decreased breath sounds, evidence of rib fractures

iii. Pelvis: Unstable pelvis, pelvic bony pain

iv. Legs: Femur fractures may have up to 1,500 mL blood loss contained in the thigh

TABLE 73.1 Circulating Blood Volume

Class	Blood Loss	Heart Rate (beats/min)	Blood Pressure	Pulse Pressure	Mental Status
	Circulating Blood Volume (%)				
1	15	<100	Normal	Normal	Uncomfortable
2	30	100-120	Normal	Narrowed	Anxious
3	40	120-140	Decreased	Narrowed	Confused
4	>40	>140	Decreased	Narrowed	Lethargic

Potential problems:

1. Patients on beta-blockade may not develop tachycardia as a response to bleeding or anemia.
2. Elderly patients have less reserve and may decompensate quickly versus children who may not develop signs of shock until severely volume-depleted.
3. Intravenous access can be difficult to obtain in patients with low circulating volume.

4. Multiple occult sources for blood loss may exist in any one patient.

Possible interventions:

1. Place two large bore IVs on all patients. Can use a large-bore, single-lumen central catheter as well, away from major areas of injury (ie, avoid femoral lines in pelvis fractures).
2. Multiple layers of gauze make tamponade more difficult. Find the source and apply directed pressure.
3. Tourniquets should not be used except in unusual circumstances and only on single bones for adequate compression (ie, humerus, femur).
4. Place a pelvic binder to control bleeding in open book pelvic fractures. Apply traction and/or splinting to control bleeding from long-bone fractures.
5. Identify intraabdominal source of bleeding with a FAST examination.

Disability or Neurologic Status

Rapid neurologic examination:

1. GCS total score (3-15)
    a. Eye opening (1-4)
    b. Motor response (1-6)
    c. Verbal response (1-5)
2. Pupillary size and reactivity
3. Lateralizing signs
4. Spinal injury level

Potential problems:

1. Intoxication can mask or reproduce symptoms of a closed head injury

2. Lucid intervals can be seen before compromise from intracranial lesions

Possible interventions:

1. Emergent neurosurgical consultation and possible intracranial monitor placement
2. Can medically control intracranial pressure with initial dose of 0.25 g/kg mannitol or 250 mL hypertonic saline after appropriate neurosurgical evaluation

Exposure/Environmental Control

1. All clothing and dressings need to be removed to inspect for injuries and examination.
2. Patients should be covered immediately after assessment to maintain warmth and prevent hypothermia that may contribute to coagulopathy.

Resuscitation

Resuscitation should begin as the patient arrives, throughout the primary and secondary surveys. The PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial compared different transfusion ratios of platelets and plasma to red blood cells. The authors conclude that there is no significant difference in mortality between the groups, but that the 1:1:1 group had a lower incidence of death secondary to exsanguination. The current recommendation for transfusion during hemorrhage is to provide a balanced resuscitation of major blood components and to target a 1:1:1 ratio.

Adjuncts to the Primary Survey

Certain interventions are important in the resuscitation of the trauma patient. These are performed as the primary and secondary surveys are being done or immediately afterward.

1. Electrocardiographic monitoring: Usually continuous on a monitor. Formal electrocardiogram may be needed if arrhythmias or possible ST-segment changes are present.
2. Pulse oximetry: Helpful in assessing perfusion status and blood oxygenation trends.
3. Urinary catheter: Assesses for blood and follow urine output. Must assess for urethral injury prior to placement (bruising at perineum, blood at meatus, high-riding prostate).
4. Gastric catheter: Assesses stomach contents for blood and evacuates stomach to lessen the risk of aspiration. Consider risk of skull base fracture with nasogastric tube in patients with facial injuries and place orally when possible.
5. Continuous blood pressure monitoring: May need arterial line if critically unstable, but this should not delay definitive care
6. Plain chest films if major blunt or penetrating trauma; pelvic films if blunt trauma or penetrating wound to abdomen. Other plain films necessity determined after the secondary survey

Secondary Survey

The secondary survey is a thorough examination and assessment of the entire patient after the primary survey is complete and resuscitation is started. The following list is not exhaustive but shows an example of what each body area examination should include.

1. History
    a. AMPLE history
        i. A: allergies
        ii. M: medications
        iii. P: past illness/pregnancy
        iv. L: last meal
        v. E: events of the injury
    b. Should include accident details or type of gun or knife used
2. Head: Lacerations, bruises, eye injuries, vision

3. Maxillofacial: Bony face instability, facial nerve injuries, and intraoral mandible fractures
4. Neck: Spine tenderness, trachea positioning off midline, and hematomas
5. Chest: Bruises, tenderness, change in breath sounds, crepitus, and uneven chest excursion
6. Abdomen: Bruising, tenderness, distention, and evisceration of bowel or omentum
7. Perineum: Vaginal tears, rectal tone, hematomas, blood at meatus, rectal bleeding, and pregnancy test in female patients
8. Limbs: Distal pulses and capillary refill, tenderness, crepitus with movement, and deformity of the limb
9. Neurologic: Detailed neurologic examination, especially spinal cord levels of injury if paralysis

Tertiary Survey

Often patients admitted to the ICU have not been fully assessed in the emergency department because of intoxication, head injury, or hemodynamic instability. It is therefore crucial that the ICU staff helps to perform a continual reassessment similar to the secondary survey as the patient stabilizes and is able to respond to the examiner. The tertiary survey must be done systematically and can often find undiagnosed fractures or other injuries. Further imaging should be performed based on symptoms or new injuries identified.

MAJOR IMMEDIATE LIFE-THREATENING CONDITIONS

After initial resuscitation and management of the most obvious injuries, more immediately life-threatening conditions may be present but undiagnosed. These may become clinically apparent once the patient has arrived in the ICU for continued care.

Tension Pneumothorax

Tension pneumothorax often presents in delayed fashion, especially if the patient is on positive pressure ventilation. Blunt or penetrating injury to the chest and line insertions during resuscitation are often the cause.

- Diagnosis:
  - Hypotension
  - Distended neck veins
  - Significant subcutaneous emphysema
  - Decreased breath sounds on one side
  - Lack of lung slide on POCUS
  - Chest x-ray (only if stable)
- Treatment:
  - Finger thoracostomy or needle decompression if unstable
  - Chest tube with closed suction drainage after needle decompression

Cardiac Tamponade

Cardiac tamponade is most often seen after penetrating injury to the chest, but it can also develop with blunt trauma, either from direct cardiac injury or fractures of the sternum or ribs.

- Diagnosis:
  - Hypotension
  - Distended neck veins
  - Diminished heart sounds
  - Echocardiography
- Treatment:
  - Pericardiocentesis: May be repeated
  - Surgery: Definitive treatment

Blunt Cardiac Injury

Blunt trauma can cause a variety of cardiac injuries, including cardiac contusion, aortic and coronary artery dissection or

transection, valve injury, chordae tendinae rupture, septal defects, and pericardial tamponade.

- Diagnosis:
  - Arrhythmias
  - Unexplained hypotension despite adequate resuscitation
  - Echocardiography
  - Cardiac enzymes (creatine phosphokinase, troponin) can be helpful to rule out blunt cardiac injury
- Treatment:
  - Inotropic agents
  - Supportive care
  - Surgery
  - Echocardiogram versus cardiac catheterization for structural assessment

Massive Hemothorax

A massive hemothorax is a large collection of blood in the chest that can lead to hemorrhagic shock as well as tension-like physiology in the chest. It can be due to major pulmonary vascular injury or blunt aortic rupture.

- Diagnosis:
  - Hypotension
  - Decreased breath sounds
  - Chest x-ray
  - Computed tomography (CT) scan of the chest with IV contrast if hemodynamically stable
- Treatment:
  - Chest tube
  - Resuscitation
  - Surgery

Other Injuries Requiring Intensive Care Unit Care

HEMORRHAGIC SHOCK

Hemorrhagic shock can quickly arise in the traumatically injured patient. A patient may have one bleeding focus or many. Differentiating this from distributive or spinal shock is also necessary, but shock secondary to continued bleeding should always be considered and treated first.

Major causes:

- Liver or spleen injuries
- Massive hemothorax
- Exsanguinating peripheral arterial injuries
- Pelvic fractures
- Long-bone fractures
- Retroperitoneal hematomas

Diagnosis:

- Known or suspected bleeding diathesis
- Anemia
- Tamponade and tension pneumothorax ruled out

Treatment:

- Rapid transfusion of blood and products as needed
- Control of bleeding through surgery, splinting, or embolization

DISTRIBUTIVE (SPINAL) SHOCK

This type of shock develops after spinal cord injury and is due to the loss of sympathetic innervation to the heart and distal vessels. It must be a diagnosis of exclusion after hemorrhagic and cardiogenic causes are ruled out.

Diagnosis:

- Known spine or spinal cord injury

- Hypotension unresponsive to appropriate fluid resuscitation
- Treatment:
  - Vasopressors and inotropes as needed, with norepinephrine as the first-line choice for mean arterial pressure (MAP) greater than 85

FLAIL CHEST

Flail chest is secondary to massive blunt injury to the chest causing fracture of at least three contiguous ribs in two or more places. It results in paradoxical movement of the chest wall during inspiration. Pulmonary contusions are often underlying the injury.

- Diagnosis:
  - Chest x-ray
  - CT scan of the chest
  - Physical examination (paradoxical motion and extreme tenderness)
- Treatment:
  - Pain control: Consider thoracic epidural
  - Pulmonary toilet
  - Intubation and ventilation if needed
  - Surgical stabilization may be helpful if slow improvement

PULMONARY CONTUSION

Pulmonary contusion is a common finding in the ICU trauma patient and ranges from mild to severe. Treatment is supportive. Pulmonary contusions usually worsen over 48 hours before improving, and that time lag is important when making future treatment decisions regarding the pulmonary system. Although the trauma patient often has massive needs for resuscitation, in patients with isolated pulmonary contusion, care should be taken to avoid fluid overload.

- Diagnosis:
  - Chest x-ray

CT scan of the chest

Treatment:

Pulmonary toilet

Supplemental oxygen

Rib plating with open reduction for displaced fractures

Intubation and protective lung ventilation with settings similar to patients with acute respiratory distress syndrome

Consider placing affected side down if significant pulmonary hemorrhage

SPLEEN AND LIVER INJURIES, PELVIC HEMATOMAS

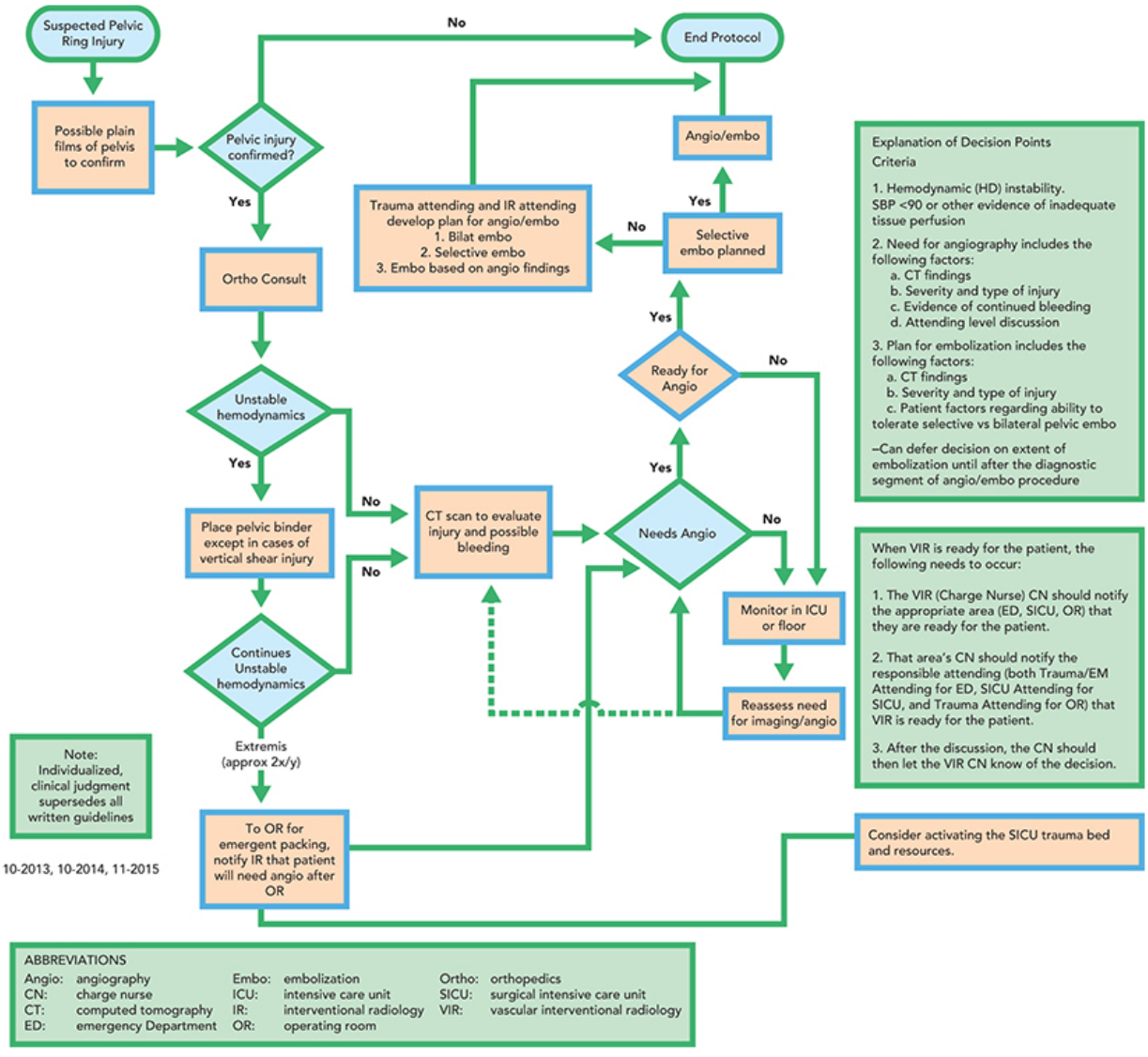
These are included together given the similarity of approach in these patients. For this group, the diagnosis is often known prior to ICU admission. The worst of these injuries that rendered the patient hemodynamically unstable have likely already been stabilized with packing or resection in the operative theater. Further management includes:

1. Serial assessment of blood counts
2. Continued resuscitation with appropriate blood products and minimal crystalloid
3. Consideration for requirement of further intervention with interventional radiology or surgery, should bleeding be persistent
4. Need for pelvic stabilization to reduce venous bleeding in pelvic fractures
5. Referral to interventional radiology for angiography/embolization should be considered in patients with pelvic fractures in the following situations:
    a. Hemodynamic instability or signs of ongoing bleeding, after nonpelvic sources ruled out
    b. Evidence of contrast extravasation on pelvic CT scan
    c. Repeat angiography with possible embolization should be considered in those who have already undergone pelvic

angiography with or without embolization, with signs of ongoing bleeding (after nonpelvic sources ruled out).

Several guidelines and treatment algorithms for the management of pelvic fracture hemorrhage have been established and updated. Algorithm 73.1 is the algorithm currently used in our institution.

ALGORITHM 73.1 **Barnes Jewish Hospital/Washington University Trauma Service Pelvic Ring Injury Protocol**


Suspected Pelvic Ring Injury
Possible plain films of pelvis to confirm
Pelvic injury confirmed?
No
End Protocol
Yes
Ortho Consult
Trauma attending and IR attending develop plan for angio/embo
1. Bilat embo
2. Selective embo
3. Embo based on angio findings
Angio/embo
Yes
No
Selective embo planned
Yes
Ready for Angio
No
Unstable hemodynamics
Yes
Place pelvic binder except in cases of vertical shear injury
No
CT scan to evaluate injury and possible bleeding
Needs Angio
Yes
No
No
Continues Unstable hemodynamics
Monitor in ICU or floor
Reassess need for imaging/angio
Extremis (approx 2x/y)
To OR for emergent packing, notify IR that patient will need angio after OR
Explanation of Decision Points
Criteria
1. Hemodynamic (HD) instability. SBP <90 or other evidence of inadequate tissue perfusion
2. Need for angiography includes the following factors:
a. CT findings
b. Severity and type of injury
c. Evidence of continued bleeding
d. Attending level discussion
3. Plan for embolization includes the following factors:
a. CT findings
b. Severity and type of injury
c. Patient factors regarding ability to tolerate selective vs bilateral pelvic embo
–Can defer decision on extent of embolization until after the diagnostic segment of angio/embo procedure
When VIR is ready for the patient, the following needs to occur:
1. The VIR (Charge Nurse) CN should notify the appropriate area (ED, SICU, OR) that they are ready for the patient.
2. That area's CN should notify the responsible attending (both Trauma/EM Attending for ED, SICU Attending for SICU, and Trauma Attending for OR) that VIR is ready for the patient.
3. After the discussion, the CN should then let the VIR CN know of the decision.
Consider activating the SICU trauma bed and resources.
Note: Individualized, clinical judgment supersedes all written guidelines
10-2013, 10-2014, 11-2015
ABBREVIATIONS
Angio: angiography
CN: charge nurse
CT: computed tomography
ED: emergency Department
Embo: embolization
ICU: intensive care unit
IR: interventional radiology
OR: operating room
Ortho: orthopedics
SICU: surgical intensive care unit
VIR: vascular interventional radiology

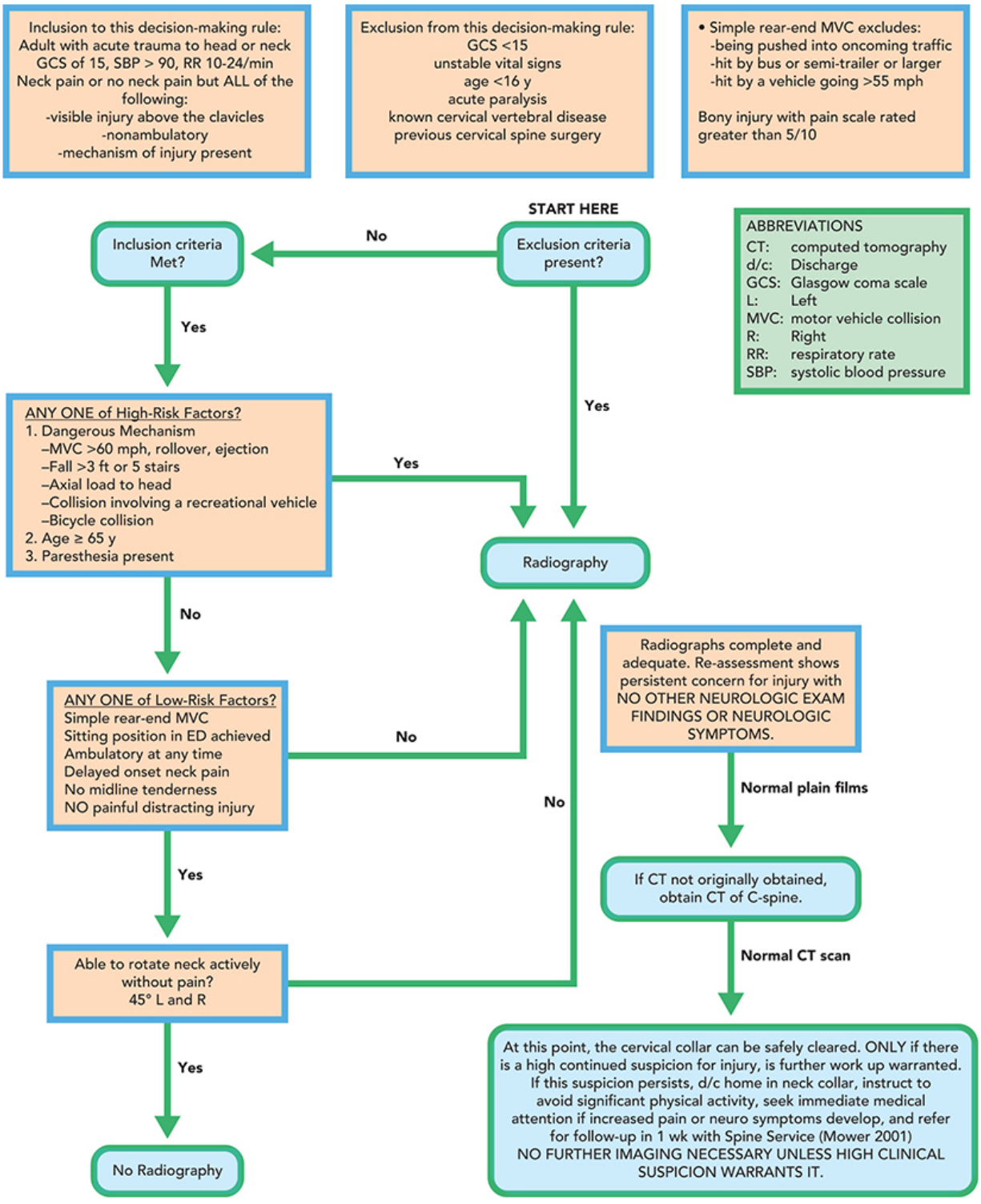
HEAD INJURY

Often patients with multiple injuries also have head injuries. Intracranial injury care is reviewed elsewhere, but treatment strategies for the multiple injured patient are often different than those for isolated head injuries. The care of these patients must involve all of the specialty teams in medical decision-making.

CERVICAL SPINE INJURY

Trauma victims are often brought to the ICU with their c-collar still in place. The collar should stay in place until an appropriate algorithm to exclude cervical spine injury has been followed. However, leaving the collar in place for an unnecessarily prolonged period of time can lead to complications due to pressure wounds and difficulty with airway management. Algorithm 73.2 is the algorithm currently used in our institution. Recently updated evidence-based guidelines are available at https://www.east.org/education-resources/practice-management-guidelines/details/cervical-spine-injuries-following-trauma.

ALGORITHM 73.2 **Cervical Spine Evaluation Guideline for Trauma Patients**


Inclusion to this decision-making rule:
Adult with acute trauma to head or neck
GCS of 15, SBP > 90, RR 10-24/min
Neck pain or no neck pain but ALL of the following:
-visible injury above the clavicles
-nonambulatory
-mechanism of injury present
Exclusion from this decision-making rule:
GCS <15
unstable vital signs
age <16 y
acute paralysis
known cervical vertebral disease
previous cervical spine surgery
• Simple rear-end MVC excludes:
-being pushed into oncoming traffic
-hit by bus or semi-trailer or larger
-hit by a vehicle going >55 mph
Bony injury with pain scale rated greater than 5/10
START HERE
Exclusion criteria present?
No
Inclusion criteria Met?
Yes
ABBREVIATIONS
CT: computed tomography
d/c: Discharge
GCS: Glasgow coma scale
L: Left
MVC: motor vehicle collision
R: Right
RR: respiratory rate
SBP: systolic blood pressure
ANY ONE of High-Risk Factors?
1. Dangerous Mechanism
–MVC >60 mph, rollover, ejection
–Fall >3 ft or 5 stairs
–Axial load to head
–Collision involving a recreational vehicle
–Bicycle collision
2. Age ≥ 65 y
3. Paresthesia present
Yes
Yes
Radiography
No
ANY ONE of Low-Risk Factors?
Simple rear-end MVC
Sitting position in ED achieved
Ambulatory at any time
Delayed onset neck pain
No midline tenderness
NO painful distracting injury
No
No
Radiographs complete and adequate. Re-assessment shows persistent concern for injury with NO OTHER NEUROLOGIC EXAM FINDINGS OR NEUROLOGIC SYMPTOMS.
Normal plain films
Yes
If CT not originally obtained, obtain CT of C-spine.
Able to rotate neck actively without pain?
45° L and R
Normal CT scan
Yes
At this point, the cervical collar can be safely cleared. ONLY if there is a high continued suspicion for injury, is further work up warranted. If this suspicion persists, d/c home in neck collar, instruct to avoid significant physical activity, seek immediate medical attention if increased pain or neuro symptoms develop, and refer for follow-up in 1 wk with Spine Service (Mower 2001)
NO FURTHER IMAGING NECESSARY UNLESS HIGH CLINICAL SUSPICION WARRANTS IT.
No Radiography

Later Complications

Although the traumatically injured ICU patient is apt to develop any of the common ICU complications, pulmonary emboli and fat emboli are more common in this population. Careful thromboembolic prophylaxis must be initiated as soon as possible with careful screening for deep venous thrombosis throughout the hospital course. Fat emboli are associated with long-bone fractures, usually after repair, and can cause severe lung disease, but are treated as most respiratory distress patients with supportive care.

Conclusion

The traumatically injured patient often requires ICU care and monitoring. Recognizing the most common life-threatening concerns quickly is important in the care of these patients. The initial survey is important to systematically identify and treat those conditions as rapidly as possible. Continuous resuscitation is the key to the survival and ultimate recovery of these patients, as well as following and recognizing the endpoints of that resuscitation.

SUGGESTED READINGS

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Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, Fourth ed. *Neurosurgery*. 2017;80(1):6-15.

Dunham CM, Barraco RD, Clark DE, et al. Guideline for emergency tracheal intubation immediately after traumatic injury. *J Trauma*. 2003;54:391-416.

Emergency tracheal intubation indicated for trauma patients with airway obstruction, hypoventilation, severe hypoxemia, severe cognitive impairment (GCS ≤8), cardiac arrest, or severe hemorrhagic shock. Emergent tracheal intubation in patients with smoke inhalation injury and the presence of: airway obstruction, severe cognitive impairment, major cutaneous burn (≥40%), moderate to severe facial/oropharyngeal burn, or moderate to severe airway injury visualized on bronchoscopy.

Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe

74 The Acute Abdomen

Marguerite W. Spruce, Lindsay M. Kranker, and Douglas J. E. Schuerer

Acute abdominal pathology is a common event in the intensive care unit (ICU) setting, yet its diagnosis is often delayed because of the absence of typical signs and symptoms of peritonitis. Though sometimes the primary reason for admission, abdominal pathologies can also develop subsequent to the patient's critical illness, such as visceral hypoperfusion or stress ulceration. Physical examination signs defining an acute abdomen, such as global tenderness, rigidity, rebound, and guarding, may not always be obvious in the ICU setting when patients have multiple ongoing medical issues. A retrospective cohort study of medical ICU patients with abdominal pathology found that surgical delay was more likely in patients with altered mental states, the absence of peritoneal signs, previous opioid analgesia, antibiotic use, and mechanical ventilation. The delay in the diagnosis and management of an acute abdomen is associated with increased mortality rates. Therefore, learning to identify an acute abdomen in a patient who is critically ill with masked physical symptoms is a lifesaving skill.

Patient History

Obtaining a history from a patient in the ICU is frequently complicated due to factors such as altered mental state, chemical sedation/analgesia, or intubation. A careful review of the patient's medical history, surgical history, allergies, and medications (especially, immunosuppressants) can provide a possible cause of the abdominal pathology. If the patient is alert, describing the pain, including its quality, onset, location, and radiation, may help to focus the differential diagnosis. Most often, the patient is not alert, requiring the collection of important medical history and preceding symptoms from family or close contacts. Exposure to antibiotics increases the risk of *Clostridium difficile* colitis. One of the most important pieces of information influencing the differential diagnosis is whether the patient has recently undergone an operation. The temporal relationship of a change in abdominal examination from the time of surgery can suggest different pathologies. For example, a patient who recently underwent abdominal surgery (<3 days) is at greater risk

of bleeding and anastomotic leak or fistula, whereas a patient a week out from surgery is more likely to have an intra-abdominal abscess.

Laboratory History

Laboratory tests are important adjuncts in the critical care setting, where most patients cannot provide an accurate history or description of their current physical symptoms. Following laboratory value trends can provide insight into an ongoing abdominal process. An increasing trend in the white blood cell (WBC) count usually signals infection or inflammation, but it is fairly nonspecific after recent surgical procedures or in patients receiving steroids. Conversely, an extreme elevated WBC (35,000-40,000 cells/mcL) can indicate a more severe infection, such as *C. difficile* colitis, and the workup should proceed accordingly. A normal or decreasing WBC count can be misleading; therefore, it is important to obtain a differential cell count and evaluate for a left shift. A decreasing WBC to leukopenic levels with a large left shift is concerning for overwhelming sepsis.

Abnormal liver function tests, including fractionated bilirubin, alkaline phosphatase, and transaminase levels, may localize pathology to the gallbladder, biliary system, or liver but are rarely diagnostic. Instead, they help guide further diagnostic strategies such as appropriate imaging. Of note, in patients who are critically ill, an acute increase in bilirubin may signify acalculous cholecystitis. Elevated amylase and lipase levels may diagnose pancreatitis, but an isolated amylase elevation may also indicate a perforated viscus or ischemic bowel. A concomitant increase in both bilirubin and amylase suggests obstruction at the distal common bile duct or pancreatic duct. Although an elevated lactate level (>4 mmol/L) may signal the emergent condition of mesenteric ischemia with necrotic bowel, it may be the result of less specific conditions such as acidemia, hypoxia, hypovolemia, anemia, or renal or liver failure. Serum lactate levels are often more useful when trended, particularly amidst resuscitation. Obtaining an arterial blood gas should determine if acidosis or hypoxemia is present and quantify the base deficit. Abdominal compartment syndrome (ACS) should be suspected in the distended abdomen when acidosis, hypoxemia, and oliguric acute kidney injury are present. Urinalysis is not specific, but microscopic hematuria or pyuria can suggest a urinary tract infection or a lower abdomen/pelvic infection.

Physical Examination

The physical examination is less reliable in a patient receiving analgesics, sedatives, or steroids, and it must focus more on changing physical examination signs rather than the traditional signs of peritonitis. In a patient whose clinical course is declining, it is important that the abdominal examination is performed serially, and a digital rectal examination is completed. The presence of abdominal scars can be corroborated with surgical history.

Because abdominal pain may be difficult to elucidate in patients who are critically ill, nonspecific signs such as tachycardia, hypotension, tachypnea, and fever raise concern for occult abdominal pathology. An increase in nasogastric output, abdominal distention, absence of bowel movements, or abrupt intolerance of enteral feeds is concerning for bowel obstruction, mesenteric ischemia, or an acute ileus due to an intra-abdominal infection. If present, hernias should be palpated to rule out incarceration or strangulation. Tachypnea can be the first sign of developing metabolic acidosis as the patient attempts to correct it with a compensatory respiratory alkalosis. This should prompt an assessment of the patient's acid-base status using chemistry and arterial blood gas, specifically focusing on the bicarbonate level and its trend over the preceding days.

Because the nursing staff spends extended periods of time with the patient, it is important to communicate with them about changes in the patient's condition. This includes information about the quantity and quality of bowel movements (*C. difficile* colitis or intestinal ischemia), the presence of distention (ACS or obstruction), drain output (abdominal sepsis, leak, or fistula), and wound drainage (intra-abdominal abscess or wound dehiscence). For a patient who has recently undergone an abdominal procedure, nonspecific signs should be concerning for some type of anastomotic leak or fistula (intestinal, biliary, pancreatic). For a patient who is about a week post-surgery, intra-abdominal sepsis, ischemia, or abscess should be considered. Salmon-colored fluid emanating from an abdominal wound can indicate fascial dehiscence.

ACS is a life-threatening condition that occurs when intra-abdominal pressure rises to a level that diminishes venous return, leading to reduced cardiac output, renal perfusion, and total lung capacity. Signs of ACS include abdominal distension, diminished tidal volumes with elevated peak pressures on the ventilator, decreased urine output, and decreased blood pressure. Bladder pressure can be transduced while the patient is paralyzed and supine; a pressure exceeding 20 mm Hg with resultant organ dysfunction

requires emergent surgical decompression. Lack of paralysis and baseline obesity can result in elevated bladder pressure.

An acute abdomen in the ICU setting may have medical or surgical consequences, and there are some diagnoses that overlap (Table 74.1). To assist in differentiating abdominal pain in patients who are critically ill in the ICU, the abdomen is best divided into six regions to help evaluate the source of abdominal pathology (Table 74.2).

TABLE 74.1 Medical Versus Surgical Causes of Acute Abdominal Pathology in the Intensive Care Unit

Medical	Workup
Acute renal failure (uremia)	↓ UOP, UA (casts), ↑ BUN and Cr, FeNa, renal ultrasound
Sickle cell crisis	↓ Hematocrit, peripheral blood smear
Adrenal insufficiency/addisonian crisis	BMP (↑ K^+, ↓ Na^+, ↓ glucose), plasma cortisol and ACTH, cosyntropin stimulation test
Spontaneous bacterial peritonitis	Ultrasound, paracentesis with Gram stain and culture
Diabetic ketoacidosis	Glucose, UA, BMP (Na^+ and K^+ levels), ABG (acidosis)
Gastroenteritis/enterocolitis	WBC,[a] stool ova/parasites
Esophagitis	EGD, barium swallow, pH monitoring
Hepatitis	LFTs, hepatitis panel
Peptic ulcer disease/gastritis	EGD, barium swallow, pH monitoring, manometry
Nephrolithiasis/pyelonephritis	UA (pyuria, hematuria), renal ultrasound
Myocardial infarction	ECG, troponins
Rectus sheath hematoma	Hematocrit, coagulation studies, CTA
Pneumonia	Chest x-ray, sputum sample, WBC
Urinary tract infection	UA (bacteria, leukocyte esterase, nitrites)
Gynecologic disease	Pelvic examination, gonorrhea/chlamydia, ultrasound

Medical	Workup
Medical and Surgical	**Workup**
Diverticulitis/inflammatory bowel disease	WBC, CT scan,[b] flexible sigmoidoscopy/colonoscopy
Clostridium difficile colitis	Stool toxin assay thrice, severely elevated WBC
Pancreatitis/pancreatic abscess	Amylase, lipase, ultrasound, CT scan to r/o necrosis
Intussusception	Ultrasound, air-contrast enema, CT scan
Intra-abdominal abscess	WBC, CT scan
Small/large bowel obstruction	WBC, lactate, plain film x-rays, CT scan
Colonic pseudo-obstruction (Ogilvie syndrome)	Lactate, electrolytes, plain film x-rays, CT scan
Choledocholithiasis	LFTs, RUQ ultrasound, MRCP
Cholangitis	LFTs, WBC, RUQ ultrasound
Mallory-Weiss tear	EGD, hematocrit, coagulation studies
Surgical	**Workup**
Acute cholecystitis	WBC, LFTs, RUQ ultrasound
Acalculous cholecystitis	WBC, LFTs, RUQ ultrasound, HIDA scan
Perforated peptic or duodenal ulcer	Plain film x-rays (free air), upper GI series, CT scan
Strangulated hernia	CT scan, lactate
Ruptured ectopic pregnancy or tubo-ovarian abscess	Beta-hCG, pelvic ultrasound
Acute appendicitis	WBC, CT scan, ultrasound to r/o other pathology
Mesenteric ischemia and necrotic bowel	WBC, lactate, ABG (acidosis), CT scan
Colonic perforation	WBC, plain film x-rays (free air), CT scan

Medical	Workup
Ruptured or leaking abdominal aortic aneurysm	Hematocrit, coagulation studies, CT angio (IV contrast)
Toxic megacolon	*C. difficile* stool toxin assay thrice, WBC, plain film x-rays, CT scan
Sigmoid or cecal volvulus	Plain film x-rays, CT scan
Boerhaave syndrome	Plain film x-rays, gastrografin swallow
Wound dehiscence	WBC, wound culture, ultrasound, CT scan
Anastomotic leak (intestinal, biliary, pancreatic)	WBC, CT scan (if patient had a recent surgical procedure)
Abdominal compartment syndrome	↓ UOP, WBC, lactate, ABG (acidosis), bladder pressures

ABG, arterial blood gas; ACTH, adrenocorticotropic hormone; BMP, blood metabolic profile; BUN, blood urea nitrogen; Cr, creatine; CT, computed tomography; ECG, electrocardiogram; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; hCG, human chorionic gonadotropin; HIDA, hepatobiliary iminodiacetic acid; IV, intravenous; LFT, liver function test; MRCP, magnetic resonance cholangiopancreatography; r/o, rule out; RUQ, right upper quadrant; UA, urinalysis; UOP, urine output; WBC, white blood cell.

[a]WBC should always be obtained with a differential cell count.

[b]CT scan should always be obtained with IV and oral contrast unless contraindication exists, that is, abnormal renal function.

TABLE 74.2 Cause of Abdominal Pathology Based on Location

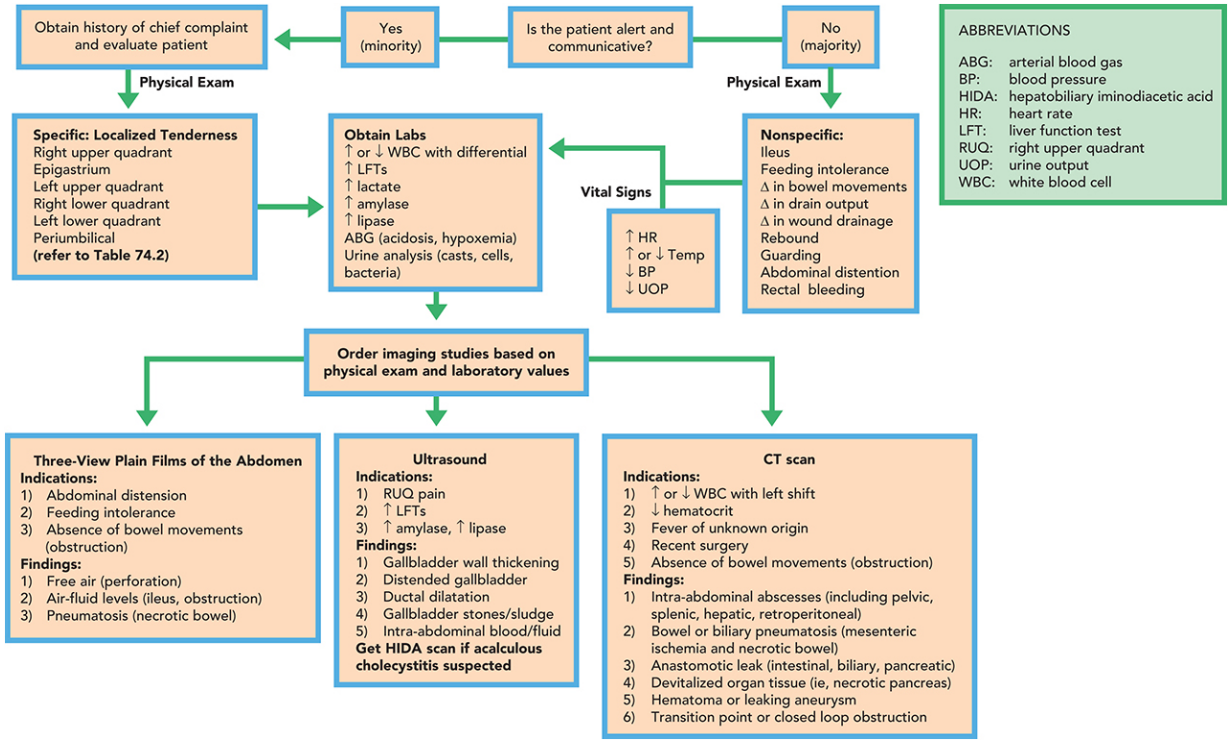
I. Right Upper Quadrant	II. Epigastrium	III. Left Upper Quadrant
Acute cholecystitis	Pancreatitis	Splenic hemorrhage or abscess
Acalculous cholecystitis	Peptic ulcer disease/gastritis	Peptic ulcer disease
Hepatitis	Perforated peptic or duodenal ulcer	Perforated peptic or duodenal ulcer
Choledocholithiasis	Mallory-Weiss tear	Pancreatitis

I. Right Upper Quadrant	II. Epigastrium	III. Left Upper Quadrant
Cholangitis	Boerhaave syndrome	Pancreatic pseudocyst or abscess
Hepatic abscess	Esophagitis	Nephrolithiasis/pyelonephritis
Pancreatitis	Gastroenteritis	Pneumonia (left lower lobe)
Peptic ulcer disease/gastritis	Myocardial infarction	
Nephrolithiasis/pyelonephritis	Pneumonia	
Appendicitis (women in pregnancy)		
Myocardial infarction		
Pneumonia		
IV. Right Lower Quadrant	**V. Periumbilical/Nonspecific**	**VI. Left Lower Quadrant**
Acute appendicitis	Enterocolitis	Sigmoid diverticulitis
Small/large bowel obstruction	Small/large bowel obstruction	Sigmoid volvulus
Cecal perforation	Mesenteric artery ischemia or occlusion	Colonic perforation
Cecal volvulus	Ruptured or leaking abdominal aortic aneurysm	Small/large bowel obstruction
Cecal diverticulitis	Early appendicitis	Enterocolitis
Enterocolitis	*Clostridium difficile* colitis or toxic megacolon	Inflammatory bowel disease
Inflammatory bowel disease	Wound dehiscence	Nephrolithiasis
Nephrolithiasis	Abdominal compartment syndrome	Urinary tract infection
Urinary tract infection	Intra-abdominal abscess	Gynecologic disease

I. Right Upper Quadrant	II. Epigastrium	III. Left Upper Quadrant
Gynecologic disease	Anastomotic leak (intestinal, biliary, pancreatic) Intussusception Spontaneous bacterial peritonitis	

An actual explanation of all possible acute abdominal emergencies and their diagnosis and treatment is beyond the scope of this chapter. An algorithm is provided to help in guiding management decisions for ICU patients experiencing intra-abdominal pathology (Algorithm 74.1).

ALGORITHM 74.1 **Diagnosis and Management of Acute Abdominal Pathology in the Intensive Care Unit**



Radiographic Examination

Imaging the abdomen helps to confirm or exclude intra-abdominal catastrophes. Initially, three plain film views of the abdomen (kidney/ureter/bladder, upright chest, and lateral decubitus) should be obtained. A dilated small bowel could indicate an ileus or small bowel obstruction, often managed nonoperatively with nasogastric decompression. However, a dilated colon is of higher concern, as a competent ileocecal valve can create a closed-loop obstruction, leading to cecal perforation that is not relieved with nasogastric decompression. Therefore, a dilated cecum on x-ray should prompt further imaging and possible surgical evaluation. The presence of air in the wall of the intestines, known as *pneumatosis*, or air in the periphery of the liver, known as *portal venous gas*, can suggest necrotic bowel, indicating the need for an emergent surgical consultation. Free air in the peritoneum or retroperitoneum suggests intestinal or gastric perforation. An unexplained pleural effusion can also point to abdominal sepsis. However, in a patient who has recently undergone laparotomy, free air should be interpreted with caution as it may be the expected result of the procedure itself.

Abdominal ultrasound is noninvasive and is the imaging modality of choice for a patient with right upper quadrant symptoms or concerning liver function tests. Ultrasound can elucidate gallbladder pathology by demonstrating pericholecystic fluid, wall thickening, gallstones, ductal dilatation, or a distended gallbladder, indicating calculous or acalculous cholecystitis. The presence of dilated bile ducts could indicate biliary obstruction, which would warrant further workup, such as magnetic resonance cholangiopancreatography (MRCP). If the concern for acalculous cholecystitis is high, a hepatobiliary iminodiacetic acid (HIDA) scan can confirm the diagnosis. Abdominal ultrasound is also useful for identifying fluid in other areas, particularly around the pancreas or in the pelvis. Although nonspecific, fluid in the pelvis may indicate intra-abdominal pathology or be a consequence of aggressive resuscitative efforts. Sonography can also evaluate for vascular occlusion, such as hepatic vein or portal venous thrombus.

Computed tomographic (CT) scanning with contrast is useful in identifying bowel thickening secondary to edema, dilated and fluid-filled intestines, fat stranding, and pneumatosis. These are all imaging signs concerning for necrotic bowel and requiring immediate surgical evaluation. CT angiography can evaluate abdominal vasculature for occlusion in the setting of acute ischemia. CT scan can also demonstrate a transition point in a bowel obstruction for easier surgical management. In a recent surgical patient with sudden clinical deterioration and a drop in hematocrit, a CT scan can reveal

an evolving hematoma or an acute bleed. Finally, CT scans are useful in identifying the location and size of intra-abdominal abscesses, guiding management through either percutaneous drainage or laparotomy and washout.

SUGGESTED READINGS

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Further reading on abdominal compartment syndrome diagnosis and management.

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Current recommendations regarding treatment of intra-abdominal infections

McBeth PB, Fabian TC. Evaluating the acute abdomen or difficult postoperative abdomen. In: Layon AJ, Gabrielli A, Yu M, Wood KE, eds. *Civetta, Taylor, & Kirby's Critical Care Medicine*. 5th ed. Lippincott, Williams & Wilkins; 2017:611-622.

Textbook chapter reviewing the general approach to a patient with an acute abdomen in the ICU.

75 Management of the Organ Donor

Louisa Yun Zhu Bai and Varun Puri

The number of patients awaiting organ transplantation in the United States continues to rise, with the current United Network for Organ Sharing (UNOS) registry showing over 100,000 patients on the waiting list. Yet, only 42,000 organs were transplanted in 2022. The increasing need is significantly greater than the number of available organs, leading to a vital shortage that results in the death of many patients awaiting organ transplantation. Different methods have been utilized in an effort to increase the number of available organs, such as expanding the donor pool to include donations from extended criteria donors and donors after cardiac death. Standardized and aggressive donor management protocols have led to increased numbers of transplantable organs from potential donors. Additionally, specialized donor centers have resulted in increased organ transplantation.

Organ Donation

The Health Care Financing Administration of the Department of Health and Human Services requires hospitals to contact the local organ procurement organization (OPO) when a patient's death is imminent, and they are deemed a suitable candidate for potential organ donation. The local OPO, in conjunction with the intensive care unit (ICU) team, establishes whether the patient meets the criteria of donor suitability. Table 75.1 summarizes various criteria for establishing the suitability for organ donation.

TABLE 75.1 Criteria for Organ Donation

Absolute contraindications:

- Age >80 years
- ABO incompatibility with the recipient
- Active hematologic malignancy, melanoma, or metastatic disease
- History of malignancy with high potential for recurrent or metastatic disease
- Untreated donor sepsis or meningitis
- Viral or parasitic encephalitis
- HIV sero-incompatability (HIV-infected donor to HIV-uninfected recipient)
- History of Creutzfeldt-Jakob disease

Relative contraindications[a]

- Active malignancy → must weigh the risk of transmission against the risks of the recipient not receiving a transplant
- Primary central nervous system tumors → can be considered for low grade I-II tumors
- HBV or HCV infection → can be considered for seropositive recipients and on a case-by-case basis
- Significant irreversible system-specific disease (ie, heart failure, interstitial pulmonary disease, cirrhosis)
- Cause of death due to massive poisoning with potential for transplanted organ nonfunction (acetaminophen, tricyclic antidepressants, carbon monoxide, cyanide, ethanol)

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
[a]Caveats to each relative contraindication noted after arrow (→).

Importantly, the clinician should avoid all discussions of organ donation with the patient's family. All communication about organ donation should occur between the OPO representative and the family. After consent is obtained, blood tests and other noninvasive tests are ordered to further evaluate whether the patient is a potential donor. Invasive procedures that may be required to further assess for organ donation should not be performed prior to the patient being declared brain dead. Brain death is established by two separate clinical examinations, apnea testing, and laboratory confirmation 24 to 48 hours apart by physicians trained in this area (specific criteria for brain death are covered in Chapter 59,

Declaration of Brain Death). If brain death cannot be established, the patient may be evaluated for potential donation after cardiac death (DCD). A summary of the process of consent for organ donation is presented in Table 75.2.

TABLE 75.2 Obtaining Consent for Organ Donation

- Contact local organ procurement organization (OPO).
- In conjunction with OPO, obtain verbal consent to perform noninvasive testing (blood sampling, ECG, radiology studies) to determine suitability for organ donation.
- Establish the diagnosis of brain death (detailed in Chapter 59, Declaration of Brain Death).
- After brain death has been declared, authorization for organ donation from family or next of kin should be obtained by a designated requestor (either OPO staff or trained hospital staff).
- If the patient is 18 years or older and has provided "First Person Authorization[a] (FPA)," legal consent is assumed and cannot be revoked by family or next of kin.
- In the absence of brain death, consider the option of "Donation after Cardiac Death" or the so-called non-heart-beating donor.

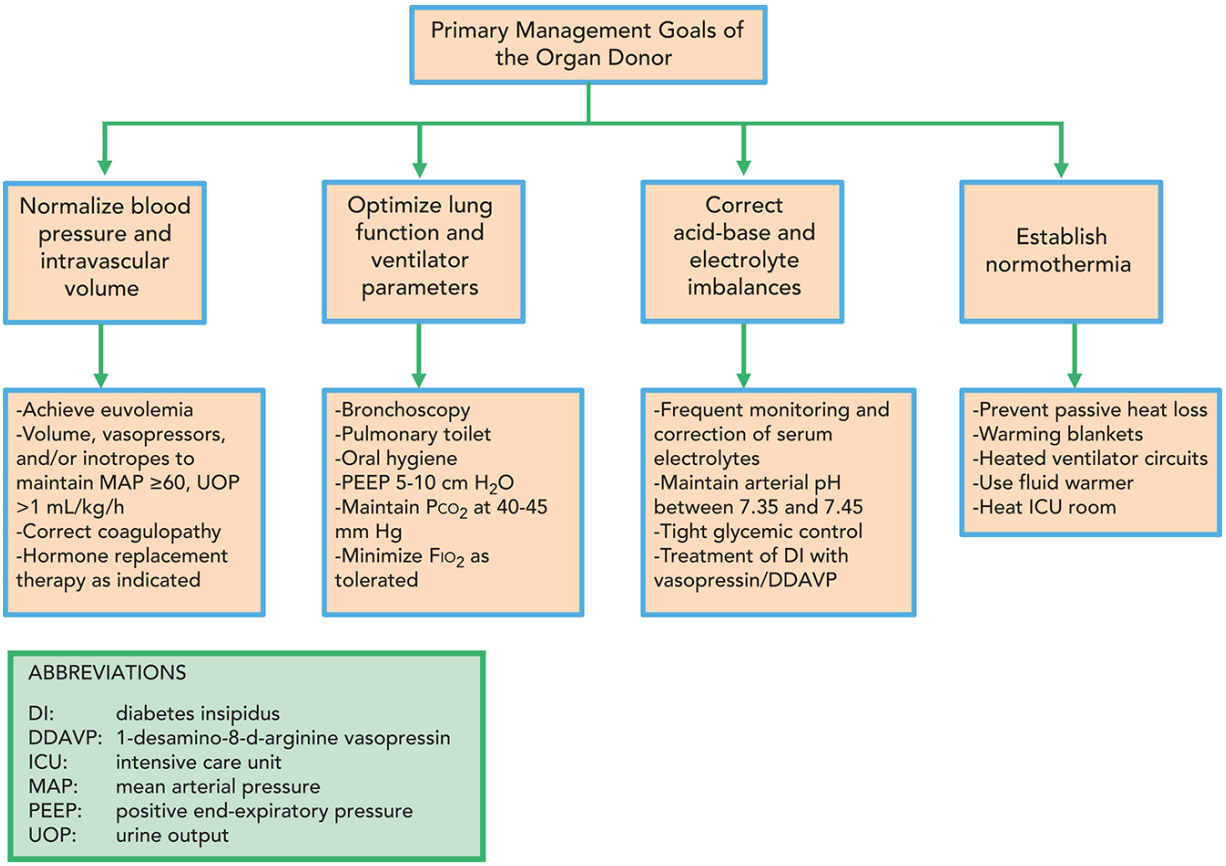
[a]First Person Authorization occurs when a person expresses their wish to be an organ donor on their driver's license, in an advanced directive, or in a donor registry, in accordance with the 2006 Uniform Anatomical Gift Act.

Certain patients require other invasive procedures to determine candidacy for potential organ donation. Examples include cardiac catheterization to evaluate coronary artery disease, lymph node biopsy to assess lymphadenopathy and for further recipient matching, and other surgical procedures to rule out malignancy for incidental findings. If preoperative procedures need to be performed, they should be coordinated between the appropriate specialist (ie, interventional cardiologist, radiologist, or surgeon) and the ICU team for optimal patient care.

Once a patient has been declared brain dead and deemed a suitable candidate for organ donation, the goals of ICU care focus on

maintaining end-organ function and perfusion. Brain death can lead to widespread hemodynamic and metabolic dysfunction with deleterious effects on organs intended for transplantation. Several clinical problems apply to donors with brain death, as well as those that are deemed potential candidates for DCD, and these are discussed in the following sections and summarized in Algorithm 75.1. Increasingly, the transplant community has been considering organ transplants using organs donated after cardiac death in the absence of brain death. Newer techniques, such as pumps to maintain kidney perfusion or ex-vivo lung perfusion, have allowed for increased organ utilization, especially in the DCD setting.

ALGORITHM 75.1 Management Goals of Organ Donor Patients


Primary Management Goals of the Organ Donor
Normalize blood pressure and intravascular volume
Optimize lung function and ventilator parameters
Correct acid-base and electrolyte imbalances
Establish normothermia
-Achieve euvolemia
-Volume, vasopressors, and/or inotropes to maintain MAP ≥60, UOP >1 mL/kg/h
-Correct coagulopathy
-Hormone replacement therapy as indicated
-Bronchoscopy
-Pulmonary toilet
-Oral hygiene
-PEEP 5-10 cm H_2O
-Maintain P_{CO_2} at 40-45 mm Hg
-Minimize F_{IO_2} as tolerated
-Frequent monitoring and correction of serum electrolytes
-Maintain arterial pH between 7.35 and 7.45
-Tight glycemic control
-Treatment of DI with vasopressin/DDAVP
-Prevent passive heat loss
-Warming blankets
-Heated ventilator circuits
-Use fluid warmer
-Heat ICU room
ABBREVIATIONS
DI: diabetes insipidus
DDAVP: 1-desamino-8-d-arginine vasopressin
ICU: intensive care unit
MAP: mean arterial pressure
PEEP: positive end-expiratory pressure
UOP: urine output

Donor Management Protocols

NORMALIZE HEMODYNAMICS

Brain death may cause cardiac dysfunction as well as vasoplegia, leading to decreased end-organ perfusion in potential donors. Cardiovascular management in the potential donor is focused on preventing hypotension (mean arterial blood pressure [MAP] <60 mm Hg) and optimizing cardiac output, while also maintaining euvolemia. Patients may require invasive lines such as central venous catheters, arterial lines, and/or pulmonary artery catheters for accurate hemodynamic monitoring.

Hypotension is frequently encountered in brain-dead patients, with initial treatment directed at volume expansion to a goal MAP of at least 60 mm Hg and urine output of at least 1 mL/kg/h. Establishing euvolemia is critical in providing adequate blood pressure and end-organ perfusion and can be guided by central venous pressure (CVP) and/or pulmonary capillary wedge pressure. Care should also be taken to avoid hypervolemia and resultant edema in the lungs, heart, and liver that may negatively impact their function post-transplant. Crystalloid solutions, colloid solutions, and blood products may be required to establish euvolemia, especially in trauma patients who commonly have excessive volume loss due to hemorrhage. Additionally, significant coagulopathy should be corrected with the transfusion of appropriate blood products (ie, platelets, fresh frozen plasma, cryoprecipitate, tranexamic acid, etc).

Persistent hypotension in the setting of adequate fluid resuscitation should prompt the placement of a pulmonary artery catheter to assess cardiac output and systemic vascular resistance (SVR). Low SVR (<400 dynes/s/cm) and decreased cardiac contractility are common causes of refractory hypotension and necessitate initiation of vasoactive or inotropic medications, respectively. Common vasoactive agents are dopamine (5-10 mcg/kg/min) or norepinephrine (2-12 mcg/min) infusions, with target MAP greater than or equal to 60 mm Hg. Brain death is associated with cardiac beta-adrenergic receptor desensitization and may

exacerbate existing causes of cardiac dysfunction in donors, such as cardiac arrest, blunt cardiac injury, or brainstem herniation. Inotropic and chronotropic agents may be used to augment cardiac function with a target cardiac index greater than 2 L/min/m^2. Agents of choice include dopamine (5-10 mcg/kg/min), dobutamine (2-5 mcg/kg/min), or epinephrine (0.05-2 mcg/kg/min).

In patients who continue to have hemodynamic instability despite adequate volume replacement and vasoactive and inotropic therapy, hormone replacement therapy is a potential option. While the mechanics are poorly understood, hormone therapy seems to stabilize the hypothalamic-pituitary-thyroid/adrenal axes, which often becomes dysregulated in brain-dead patients due to brainstem injury and deficiencies in thyroid hormone and cortisol. Hypotensive donors receiving vasopressors greater than 10 mcg/kg/min should receive thyroid hormone (20 mcg, then 10 mcg/h of T4), hydrocortisone (300 mg, then 100 mg every 8 hours), and/or vasopressin (1 unit, then 0.01-0.1 units/min), titrated to MAP greater than or equal to 60 mm Hg.

Hypertension and tachycardia may be present due to excess sympathetic activity (or “autonomic storm”) in brain-dead patients and should be treated to decrease the risk of subsequent myocardial dysfunction. Short-acting agents such as esmolol or nicardipine are preferred as these disturbances are often transient and may be followed by profound hypotension.

OPTIMIZE PULMONARY FUNCTION

Pulmonary function is critical in all organ donors to help maintain adequate gas exchange but is especially vital in potential lung donors. Common practices that help improve pulmonary function include frequent airway suctioning, chest percussion, and patient turning. Bronchodilator therapy can help with airway clearance, prevention of atelectasis, and avoidance of pulmonary edema. Bronchoscopy is helpful both in a diagnostic setting—assessing for aspiration, infection, or trauma—and in the therapeutic setting—optimizing pulmonary function via clearance of mucus plugs and

secretions. Additionally, good oral hygiene and head-of-bed elevation to 30° can help prevent ventilator-associated pneumonia.

Mechanical ventilation in patients should be tailored to prevent atelectasis, pneumonia, and pulmonary edema. Brain-dead patients may develop pulmonary edema that is attributable to systemic inflammatory and neurogenic responses. Positive end–expiratory pressure (PEEP) can be used with a target of 5 to 10 cm H_2O to offset the increased capillary permeability associated with pulmonary edema, as well as to maintain alveolar expansion. However, PEEP levels higher than 10 cm H_2O can result in impaired venous return, which negatively impacts cardiac output. Ventilator settings should be optimized to maintain arterial P_{CO_2} at 40 to 45 mm Hg and plateau pressure <30 mm Hg. Lung-protective ventilation, with low tidal volume and high PEEP, has been shown to increase the number of lungs eligible for transplantation. If hemodynamics and acid-base status allow, tidal volumes should be maintained between 6 and 8 mL/kg of predicted body weight. Fraction of inspired oxygen should be less than or equal to 0.6 whenever possible to minimize oxygen toxicity. Additionally, recruitment maneuvers (with PEEP up to 15 cm H_2O) may be helpful to minimize atelectasis. Placing potential lung donors in the prone position may address basal atelectasis and improve oxygenation.

Hypervolemia should be avoided in patients who are potential lung donors. Judicious volume administration, often guided by CVP or pulmonary artery catheter information, to achieve end-organ perfusion should be balanced against the accumulation of extravascular fluid in the lungs.

CORRECT ACID-BASE AND ELECTROLYTE DISTURBANCES

Brain-dead patients can frequently develop polyuria, with urine outputs greater than 500 mL/h. The causes of polyuria can be multifactorial, including physiologic, osmotic, pharmacologic, or hypothermic diuresis, as well as central diabetes insipidus (CDI). Uncontrolled diuresis can lead to profound electrolyte disturbances

such as hypernatremia, hypokalemia, and hyperosmolality. To avoid cardiac dysfunction, electrolytes and serum osmolality should be frequently monitored and corrected to be within a normal range. Serum sodium should be maintained between 135 and 155 mEq/dL and serum potassium between 4 and 5 mEq/dL. Arterial pH should be maintained between 7.35 and 7.45, which can be accomplished by judicious hyperventilation and/or sodium bicarbonate administration. Protocol-driven continuous insulin infusions are also necessary to maintain tight glucose control (120-180 mg/dL), which prevents significant hyperglycemia-related osmotic diuresis.

When polyuria is associated with elevated serum sodium and other readily reversible causes of polyuria are excluded, the likely diagnosis is CDI. Other features include increased serum osmolality and inappropriately dilute urine (urine osmolality <200 mOsm/kg H_2O). This is often due to ischemia of the posterior pituitary gland secondary to direct brain trauma or hypoperfusion. In the setting of a potential organ donor, a water deprivation test is impractical and unnecessary to establish the diagnosis. Instead, empiric treatment can be initiated with intravenous vasopressin or 1-desamino-8-d-arginine vasopressin (DDAVP), titrated to maintain a urine output of 0.5 to 1 mL/kg/h. Vasopressin is helpful if there is concomitant hypotension due to its additional vasoactive effects, while DDAVP is highly selective for the V2 receptors on kidney tubules and can be used for patients with normal hemodynamics. Correction rate of sodium should be limited to 0.5 mEq/L/h to avoid further cerebral edema. Frequent electrolyte and hemodynamic monitoring are essential to correct further imbalances.

MAINTAIN NORMOTHERMIA

Thermoregulation in healthy individuals is controlled by the hypothalamus. Hypothalamic dysfunction and decreased compensatory responses (ie, shivering, vasoconstriction) in brain-dead patients often lead to hypothermia. Passive heat loss and treatment with unwarmed fluids and blood products also exacerbate hypothermia in potential organ donors. Hypothermia should be

managed aggressively to minimize associated coagulopathy, cardiac dysfunction, arrhythmia, and leftward shift of the oxyhemoglobin dissociation curve. Target body temperatures of 36 to 37.5 °C should be achieved. Additionally, severe hypothermia precludes the determination of brain death. Measures to prevent hypothermia include warming the ICU room to >75 °F, forced-air warming blankets, administration of warmed fluids, and warming of ventilator circuits.

Specialized Donor Care Facilities

Donor procurement was traditionally performed with transplant surgeons from different recipient centers traveling to the organ donor's hospital, often involving operating room staff not specifically trained for multiorgan procurement surgery. Given the complex coordination between multiple procurement teams and the variability in donor management at individual hospitals, specialized donor care facilities (SDCF) have been created. Brain-dead donors are transferred to these facilities equipped with an ICU and surgical suite for further workup and management prior to organ harvest. In 2001, Mid-America Transplant in St. Louis, Missouri became the first OPO to open an onsite SDCF, which contains an operating room, tissue recovery room, cardiac cath lab, six-bed ICU, and staff specially trained for organ donor management and procurement. It is located within 5 miles of both transplant centers in the OPO's encatchment area. Since then, nearly 20% of OPOs nationwide have opened onsite SDCFs.

SDCFs provide multiple benefits. For local procurements, cold ischemia time is reduced, travel time is reduced, and more procurements can occur during daylight hours. Additionally, these facilities allow for the institution of organ-specific donor management protocols, which have been shown to increase lung procurement rates (from 20% to 34%). Organ procurements at SDCFs have a higher overall yield compared to organ procurements at hospitals (28% increase). Standard criteria and extended criteria donor organ

yield were also higher than the national average (by 6% and 18%, respectively). Additionally, these facilities allow for more efficient procurements and a 50% decrease in donor recovery cost compared to in-hospital recovery.

Summary

The focus of management for a potential organ donor is centered on preserving end-organ function and viability. Standardized aggressive donor management protocols and specialized donor centers have been shown to increase the rates of organ procurement. After consent is obtained and the patient meets the criteria for donation, care should be focused on maintaining normothermia and hemodynamic stability, restoring intravascular volume, optimizing lung function, and correcting acid-base and electrolyte disturbances. Diligent management of these systems minimizes the deleterious effects of brain death on organs suitable for transplant and potentially improves long-term allograft function. Many of the steps outlined in this chapter are also suitable for preserving the viability of organs procured from DCD donors in the absence of brain death.

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SECTION XVIII NUTRITION IN THE ICU

76 Nutrition in the Intensive Care Unit

Beth Taylor, Jeffrey Pepin, and Dominic Reeds

Nutrition support is critical to intensive care unit (ICU) care. The four cornerstones of nutrition care include nutrition assessment, nutritional risk determination, nutrition prescription and initiation, and monitoring of nutrition support. This process should begin at the time of patient admission. Early identification of malnutrition is important because it is common, affecting ~15% of hospitalized patients, worsens morbidity and mortality, and its effects on outcomes can be ameliorated with appropriate nutritional support. Critical illness is associated with large-scale changes in macronutrient metabolism, particularly protein turnover, which increases the risk of malnutrition. Importantly, the underlying cause of the critical illness (eg, surgery, sepsis, burn injury) affects the timing, energy content, and macronutrient composition of nutritional interventions. Providing nutrition support tailored to the individual patient can favorably impact the nutritional status, attenuate loss of lean body mass, and improve morbidity and mortality.

Nutrition Assessment and Risk Determination

Nutrition assessment and risk determination should be performed using a validated tool at the time of admission and at regular intervals during the hospital course because patients initially identified as low risk or well-nourished may transition to high risk or become malnourished. Nutritional risk refers to patients who are at increased risk of developing acute malnutrition that, when combined with their underlying medical condition, may adversely impact clinical

outcomes. Currently, three tools to assess nutritional risk have been validated in critically ill patients, the Nutritional Risk Screening (NRS) 2002, Nutritional Risk in Critically Ill (NUTRIC) score, and mNUTRIC score. The mNUTRIC (modified NUTRIC) score, which waives the requirement for determining interleukin-6, and the NRS 2002 are both easy to use, increasing their routine clinical applicability (Table 76.1). The mNUTRIC has been validated in several critically ill patient subsets including burns, severe acute pancreatitis, abdominal surgery, severe pneumonia, and COVID-19.

TABLE 76.1 Parameters for High Nutrition Risk and Severe Acute Malnutrition

Severe Acute Malnutrition ***(At Least Two of Following Are Present)***	**NRS 2002** ***Total Score ≥5 = High Risk***	**mNUTRIC Score** ***Total Score ≥5 = High Risk***
Energy intake ≤50% of need for 5 d or more	Energy intake for 7 d: 1 point: <50%-75% 2 points: 25%-50% 3 points: 0%-25%	Age (years) 0 point: <50 1 point: 50-74 2 points: >75
Weight loss: >2% in 1 wk, >5% in 1 mo, >7.5% in 3 mo	Weight loss 1 point: >5% in 3 mo 2 points: >5% in 2 mo (BMI 18.5-20.5) 3 points: >5% in 1 mo (BMI <18.5)	APACHE II 0 point: <15 1 point: 15-19 2 points: 20-27 3 points: ≥28

Severe Acute Malnutrition ***(At Least Two of Following Are Present)***	**NRS 2002** ***Total Score ≥5 = High Risk***	**mNUTRIC Score** ***Total Score ≥5 = High Risk***
Moderate fat loss muscle wasting and/or peripheral edema	Diagnosis 1 point: chronic condition 2 points: acute condition 3 points: head injury, BMT, ICU patient	SOFA 0 point: <6 1 point: 6-9 2 points: ≥10 No. of comorbidities 0 point: 0-1 1 point: ≥2 Days from hospital to ICU admit 0 point: 0-1 1 point: ≥1

Decreased functional status.
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; BMT, bone marrow transplant; ICU, intensive care unit; mNUTRIC, modified nutritional risk in critically ill; NRS, nutritional risk screening; SOFA, sequential organ failure assessment.

Patients diagnosed with moderate-to-severe malnutrition or identified as high nutrition risk should undergo a complete assessment to achieve a patient-tailored nutrition intervention. The critical care dietitian will interpret the components of the nutrition assessment including a nutrition-focused physical exam (NFPE), diet history (specifically recent intake to determine the risk of the refeeding syndrome [RFS]), biochemical data (complete metabolic panel, magnesium, phosphorus, complete blood cell [CBC], and micronutrients guided by the clinical scenario), anthropometrics (height, weight, and recent weight changes) functional status, and social history including food availability and alcohol use. The severity (mild <5%, moderate 5%-10%, and severe >10%) of unintentional weight loss during the 3 months prior to hospital admission is a strong predictor of outcomes. Results of the nutrition assessment and level of nutrition risk should be incorporated into the decision-making of the patient's overall ICU care plan.

Nutrition Monitoring

The hospital team should ensure ongoing monitoring of NFPE, potential drug-nutrient interactions, metabolic complications, and patient safety issues (eg, monitoring electrolytes for risk of RFS, glycemic control). Plasma albumin and prealbumin are prognostic factors but are not recommended for initial or ongoing assessment of nutritional status or the adequacy of nutrition support. Both are negative acute-phase reactants and thus are influenced by critical illness itself, with alteration in albumin synthesis and degradation and increased capillary losses as a result of inflammation. Objective assessment of skeletal muscle mass in the ICU is challenging. New technology with serial ultrasound measurements shows promise as a simplistic bedside tool that can be used to assess change in muscle volume over time.

Nutrition Prescription and Initiation

The nutrition prescription should incorporate the determination of the patient's daily estimated calorie, macronutrient, and micronutrient requirements (eg, grams of protein, vitamin supplementation), the composition of the diet (required disease-specific changes), and instructions for the provision and route of delivery of nutrition support. The patient's ideal body weight (IBW) and body mass index (BMI) should be determined to aid with an assessment of calorie and protein requirements (Table 76.2). Measuring energy expenditure in critically ill patients is challenging; while technology has improved to allow for more frequent bedside indirect calorimetry measurements, high cost and inaccuracy with inspired oxygen concentrations >60% have prohibited widespread use. Few equations to assess energy expenditure have been studied exclusively in critically ill patients. The two most commonly used, the Ireton-Jones and Penn State equations, are cumbersome to complete, prompting guidelines to support the use of more simplistic weight-based formulas

(Table 76.3). Caution should be taken with weight-based prediction formulas, especially in extremes of weight (cachexia and extreme obesity), pregnancy, and hypermetabolic states (eg, severe burns). The lower range in each category should be considered in insulin-resistant patients to decrease the risk of hyperglycemia and infection associated with overfeeding; this is most common in patients with patients with underlying type 2 diabetes, treatment with glucocorticoids, or obesity. In critically ill patients with obesity (BMI ≥30), hypocaloric, high-protein feeding is recommended.

TABLE 76.2 Body Mass Index and Ideal Body Weight Calculations

Body Mass Index	Ideal Body Weight
Weight (lbs) × 704/in^2 Weight (kg)/m^2	Men: 106 lbs for first 5 ft plus 6 lbs for each inch above 5 ft Women: 100 lbs for the first 5 ft plus 5 lbs for each inch above 5 ft

TABLE 76.3 Weight-Based Energy Needs

Body Mass Index (kg/m^2)	Energy (kcal/kg/d)[a]
<15	35-45
15-19	30-35
20-24	25-30
25-29	20-25
30-50	11-14
>50	22-25/kg ideal body weight

[a]kg, actual weight or estimated dry weight unless otherwise specified.

Protein needs should be determined using either the patient's actual body weight, estimated dry weight in the setting of fluid overload conditions (eg, ascites), or IBW in patients with obesity. Data suggest that prescribing protein above that of the US recommended daily amount, up to 1.5 g/kg/d, did not improve time-to-discharge alive in medical ICU patients (Table 76.4). High protein provided to patients with high severity of disease and acute renal injury may be harmful. Protein requirements in critically ill burn, surgical, and trauma patients, and patients with obesity require continued study. Changes in protein metabolism associated with critical illness combined with conditions that lead to increased losses, including burns, large open wounds, temporary open abdomen closure, and continuous renal replacement therapy for acute kidney injury (AKI), may increase the requirements for protein (Table 76.5).

TABLE 76.4 Recommended Daily Protein Intake

Clinical Condition	Protein Needs (g/kg ABW/d)
Medical ICU	1.0-1.3
Surgical/neurology ICU	1.2-2.0
Acute kidney injury	
No dialysis	0.9-1.2
HD/SLED	1.2-1.5
CRRT	1.5-2.0
Hepatic failure	1.0-1.3[a]
Trauma	
General	1.5-2.0

Clinical Condition	Protein Needs (g/kg ABW/d)
Traumatic brain injury	1.5-2.0
Open abdomen	1.5-2.0 (+15 g/L/exudate)
Burn	1.5-2.0
Sepsis	1.2-2.0
BMI 30-40	2.0-2.5[b]
BMI >40	2.5[b]

Clinical conditions are not additive; to calculate needs, use the value that prescribes the highest protein needs.

ABW, actual body weight; BMI, body mass index; CRRT, continuous renal replacement therapy; HD, hemodialysis; ICU, intensive care unit; SLED, sustained low-efficiency dialysis.

[a]Use dry weight.

[b]Use ideal body weight.

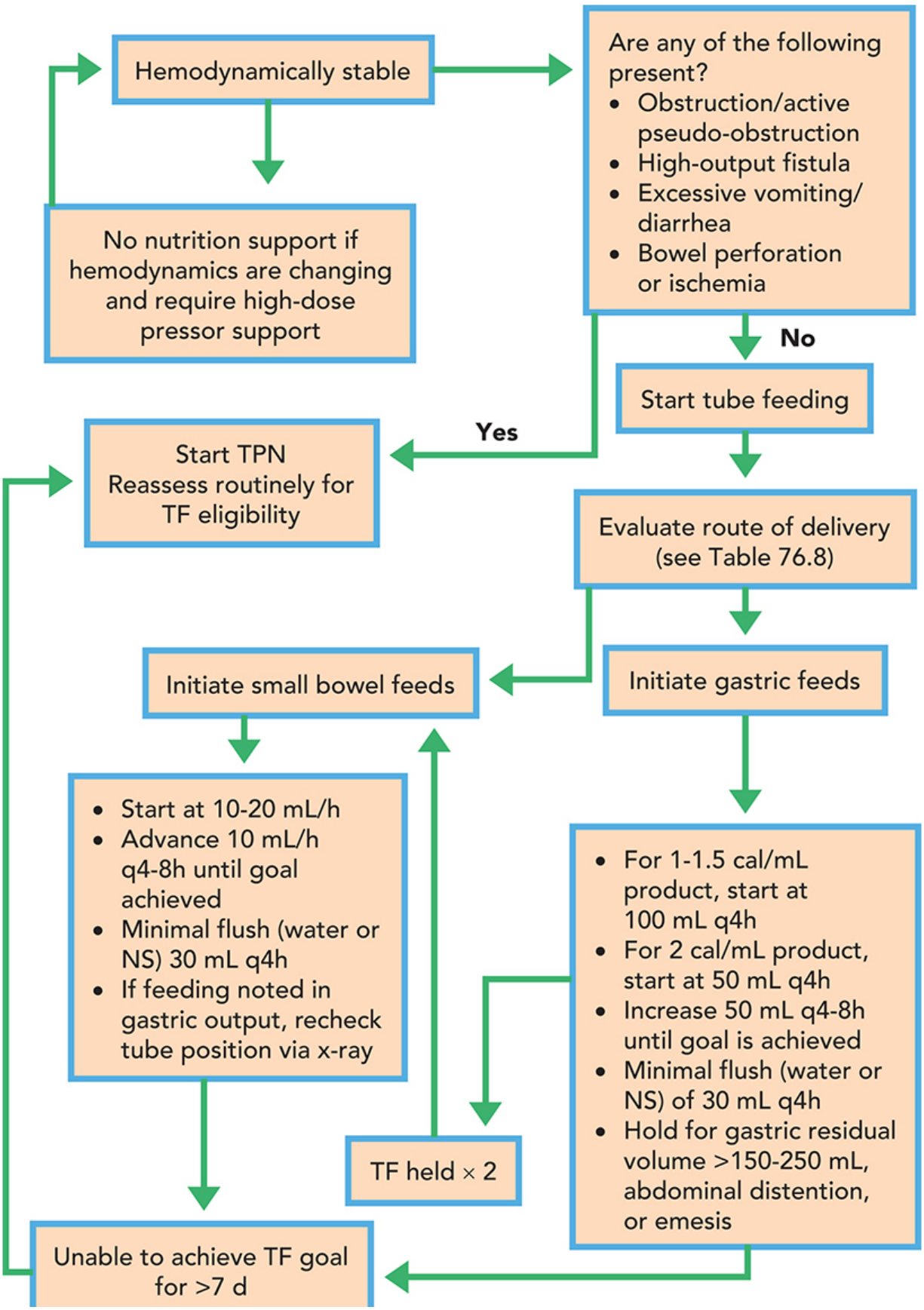
TABLE 76.5 Advantages and Disadvantages of Enteral and Parenteral Nutrition

Type of Feeding	Advantages	Disadvantages
Enteral nutrition	Preserves gut mucosal integrity Less costly than TPN May blunt hypermetabolic response	Requires functional GI tract More time to reach goal calories Multiple contraindications (eg, obstruction, fistula)
Parenteral nutrition	Does not require functioning GI tract Full therapy in <24 h	Intestinal atrophy Requires central IV access Increased rate of infectious complications

GI, gastrointestinal; IV, intravenous; TPN, total parenteral nutrition.

The nutrition prescription should include the optimal route of delivery (Algorithm 76.1). In general, enteral nutrition (EN) is preferred over parenteral nutrition (PN) because it is less expensive, may improve gut function, and does not require placement of central venous access. Despite the perceived risk of bloodstream infection with PN, recent literature suggests that survival outcomes do not differ on the basis of the route of feeding. If initiating EN, either gastric or small bowel feeding is acceptable, with the majority of ICU patients able to be fed gastrically. In critically ill patients with gastric feeding intolerance (patient complaints of pain, vomiting, or abdominal distention), early placement of a small bowel feeding tube should be considered. Patients who may benefit from the early placement of a postpyloric feeding tube are presented in Table 76.6.

ALGORITHM 76.1 **Determination of Route and Initiation of Feeding**


Hemodynamically stable
Are any of the following present?
• Obstruction/active pseudo-obstruction
• High-output fistula
• Excessive vomiting/ diarrhea
• Bowel perforation or ischemia
No nutrition support if hemodynamics are changing and require high-dose pressor support
No
Start tube feeding
Yes
Start TPN
Reassess routinely for TF eligibility
Evaluate route of delivery (see Table 76.8)
Initiate small bowel feeds
Initiate gastric feeds
• Start at 10-20 mL/h
• Advance 10 mL/h q4-8h until goal achieved
• Minimal flush (water or NS) 30 mL q4h
• If feeding noted in gastric output, recheck tube position via x-ray
• For 1-1.5 cal/mL product, start at 100 mL q4h
• For 2 cal/mL product, start at 50 mL q4h
• Increase 50 mL q4-8h until goal is achieved
• Minimal flush (water or NS) of 30 mL q4h
• Hold for gastric residual volume >150-250 mL, abdominal distention, or emesis
TF held × 2
Unable to achieve TF goal for >7 d

ABBREVIATIONS

TF : tube feeding
TPN: total parenteral nutrition

TABLE 76.6 Gastric and Small Bowel Feeding Indications

Gastric Feeding	Small Bowel Feeding
Majority of ICU patients Short gut	Delayed gastric emptying Postoperative gastric ileus Proven intolerance to gastric feeding Severe acute pancreatitis Intolerant to gastric feeds Requiring gastric decompression

ICU, intensive care unit.

Despite efforts, the majority of ICU patients receive well below the prescribed amount of EN for a variety of reasons including interruption of procedures. Measures should be taken to continue EN if non-life-threatening complications arise as noted in Table 76.7. Daily surveillance of gastric residual volume (GRV) is no longer recommended as it does not correlate with aspiration risk or clinical outcome and reduces nutrient delivery to inappropriate holding of EN. Volume-based feeding protocols pivot from an hourly goal to a daily goal of EN volume and may be useful in patients with frequent feeding interruptions, such as those with increased diagnostic testing or trips to the operating room.

TABLE 76.7 Troubleshooting Tube Feeding Complications

Residuals: Should not be routinely used. If used, a volume of 500 mL should be correlated with clinical signs of intolerance: abdominal distention, fullness, discomfort, or presence of emesis. If present consider:

- Repeat radiograph to confirm the position of tube or check pH of the contents.

- Start a prokinetic agent: IV metoclopramide 10 mg q6h (if no renal failure present), for no greater than 72 h.
- Change to a more calorically dense product to decrease the total volume infused.
- Order a small bowel feeding tube.

Diarrhea: Quantify the amount of stool. May have 4-5 loose stools per day on EN. If present consider:

- Review medications. Diarrhea may be secondary to an enteral medication. Try changing the medication route to IV.
- Rule out the presence of *Clostridium difficile*.
- Try adding soluble fiber to feeds (10-20 g in divided doses over 24 h) if the patient fully resuscitated and without risk of bowel ischemia. (no fiber on GI surgery patients for 1 wk).
- Once the infectious cause is ruled out, use an antidiarrheal agent (loperamide 2-4 mg q6h).
- Keep feeding.

Constipation: Difficulty passing or no bowel movement >3 d after feedings are at goal.

- Start bowel regimen per hospital protocol.
- Check for signs of dehydration, such as hypernatremia, prerenal azotemia, oliguria, low skin turgor, and orthostatic hypotension.
- Order KUB to rule out obstruction.
- Increase the amount of free water.
- Rectal examination with disimpaction
- Once obstruction is ruled out, consider suppository and/or enema as PRN.

EN, enteral nutrition; GI, gastrointestinal; IV, intravenous; KUB, kidney/ureter/bladder x-ray; PRN, as needed.

EN started in the acute phase of critical illness (<24-72 hours) may protect gut mucosal integrity by maintaining villous height and supporting immuno-globulin A (IgA)-producing immunocytes, which comprise the gut-associated lymphoid tissue (GALT); however, this may be challenging due to gut dysmotility. If the use of EN is not feasible or 80% of goal feeding is not achieved, PN should be considered as a supplemental or primary source of nutrition, starting within 5 to 7 days in low nutrition risk patient or earlier in patients with evidence of severe acute malnutrition or high nutrition risk.

The European Society for Parenteral and Enteral Nutrition (ESPEN) suggests that the metabolic stages of critical illness can be considered in the context of the acute phase (days 1-7) and the recovery phase (day >7). The acute phase is further divided into early (days 1-2) and late acute phases (days 3-7) and is hallmarked by catabolism and metabolic and hemodynamic instability. During the acute early phase, caloric targets for either EN or PN are recommended to be set at ~25% to 50% of usual caloric goals (eg, ~12.5 kCal/kg), while during the acute late phase, caloric targets set at ~50% to 70% of estimated energy targets (eg, ~17.5 kCal/kg) or 80% to 100% of measured energy requirements are recommended. During the recovery phase of ICU, day >7, caloric targets should be set at 80% to 100% of estimated or measured energy requirements. Phasing critical illness based simply on the duration of stay may be problematic as it is unclear when a patient transitions between each phase of critical illness. There is a paucity of safety data for early EN in patients with septic shock, although a recent review found that the gravest complication, nonocclusive bowel necrosis, was uncommon with a rate of 0.3%. There is no direct evidence on how to initiate and progress EN in patients with septic shock. Three multicenter randomized controlled trials, including patients with septic shock and comparing lower and higher rates of EN delivered within the first week of critical illness, found no difference in clinical outcomes, suggesting delivering restricted-energy EN during this time may be reasonable.

The composition of the EN formula chosen is influenced by the clinical status and comorbidities of the critically ill patient. EN formulas can be divided into four general categories: standard polymeric, elemental/semi-elemental, disease-specific, and immune-modulating; also, within each category choices with differences in calories and protein per set volume exist. Based on the current evidence, standard polymeric formulas (intact proteins, long-chain triglycerides [LCT]) are recommended unless symptoms of malabsorption are present, and then a semi-elemental (predominantly peptides 10-40 amino acids in length, simple sugars, and shorter chain glucose polymers, higher ratio of medium chain

triglycerides to LCT) product should be considered. Elemental formulas (high content of free amino acids, short-chain glucose moieties, extremely low in fat) may be considered in patients with overt fat malabsorption or a chyle leak. Disease-specific formulas include those that have been altered in their macro- or micronutrient content to address the needs of a specific disease (diabetes, hepatic insufficiency, pulmonary failure, and renal failure). In general, the clinical advantage of disease-specific formulas over less-expensive, standard, or semi-elemental formulas has not been proven. Studies using immune-modulating formulas (those enriched with glutamine, arginine, omega-3 fatty acids, antioxidants, or nucleotides) are associated with improved clinical outcomes in trauma and postoperative patients. The use of immune-modulating formulas has not been established in patients with severe sepsis or general medical ICU patients, and evidence does not strongly support the use of fish oil and/or antioxidants in acute respiratory distress syndrome (ARDS) or severe acute lung injury populations. Insoluble fiber should be avoided in all critically ill patients, and soluble fiber should only be used in resuscitated, hemodynamically stable patients. Both forms of fiber should be avoided in patients with severe dysmotility or at risk of bowel ischemia.

EN access devices vary in the type of construction material, length and diameter, presence of a stylet or guidewire, number of lumens, and the presence of a Y-port. In general, all tubes designed for EN are completely radiopaque or have a radiopaque strip to facilitate radiographic confirmation of placement. Critically ill patients presenting with injuries (eg, traumatic brain injury) or conditions that will clearly require more than 4 weeks of EN therapy will benefit from the early placement of long-term feeding access. For conditions requiring less than 4 weeks of therapy, placement of short-term feeding access via the nose or mouth should be instituted. Several options for both short- and long-term access and their associated risks are reviewed in Table 76.8.

TABLE 76.8 Short- and Long-Term Enteral Feeding Access

- **Salem sump nasogastric or orogastric:** a short-term feeding tube generally placed by the bedside nurse for decompression that may be used for feeding. The patient must have a functioning GI tract, adequate gastric emptying, and a low risk of aspiration. Nasally placed tubes carry the risk of sinusitis and nasal necrosis.
- **Nasoenteric feeding tube** for gastric or small bowel placement: a short-term, softer, more flexible tube with less risk of causing sinusitis or nasal necrosis; this tube may also be placed orally. Generally placed in patients for comfort. Small bowel tubes are placed in patients with poor gastric emptying and have a high risk of reflux.
- **G-tube**[a] for surgical or percutaneous endoscopic gastrostomy: a long-term feeding tube for patients with a functioning GI tract and adequate gastric emptying. G-tubes have a lower risk of aspiration when compared with above-the-diaphragm feeding access.
- **J-tube**[a] for surgical or percutaneous endoscopic jejunostomy: a long-term feeding tube indicated for patients with a functioning GI tract, poor gastric emptying, and a high risk for reflux and aspiration.
- **G-J tube**[a]: a long-term feeding tube placed percutaneously or at the time of laparotomy in patients for feeding into the distal duodenum with a gastric port for decompression.

GI, gastrointestinal.

[a]All tubes that transverse the two epithelial barriers of the skin and mucosa of the GI tract carry the risk of hemorrhage and infection at the incision site as well as peritonitis and risk of dislodgment.

Due to its hypertonicity, PN must be administered via a designated port of a central venous catheter. The choice of catheter type depends on the reason for PN, the expected duration of need, and the patient's clinical status (Table 76.9). In the absence of signs or symptoms of bacteremia, a newly placed catheter is not required as long as a designated port is available with the existing access. Minimizing blood draws from the lumen used for PN and strict adherence to line hygiene protocols reduce the risk of catheter-associated bloodstream infections. Partial PN via a peripheral intravenous line is not appropriate for the critically ill patient and is poorly tolerated with frequent early sclerosis of the vein. Use of

femoral lines for PN should be avoided unless emergently needed because of the high rate of infections and thrombosis.

TABLE 76.9 Catheter Selection for Total Parenteral Nutrition

- **Triple/quad lumen catheter:** used for in-hospital patients on TPN. The distal port is preferred for the infusion of TPN solution to maintain sterility and avoid contamination. Blood is drawn through the medial port, and other infusions are performed through the proximal port(s).
- **PICC:** PICC lines are placed via the brachiocephalic vein. PICC lines have a long catheter (60 cm) with the tip positioned in the superior vena cava.
- **Tunneled catheter:** This is a silastic catheter (single-, double-, or triple-lumen) that is tunneled subcutaneously several centimeters from the insertion site before exiting the skin. If no infection is present, these catheters can stay in place indefinitely.
- **Hohn:** A percutaneously placed catheter used for patients requiring 6 mo or less of TPN or IV medication. The distal port (red) is preferred for the infusion of TPN solution to maintain sterility and avoid contamination.
- **Implanted venous access device:** This is a subcutaneously implanted chamber attached to a silastic central venous catheter, either single or double lumen. Because the reservoir is implanted, it must be accessed with a needle for drawing blood or administering TPN or other IV infusions. These catheters are generally reserved for patients receiving chemotherapy who require periodic infusions.

IV, intravenous; PICC, peripheral inserted central catheter; TPN, total parenteral nutrition.

The practitioner prescribing and monitoring the patient on PN must be knowledgeable regarding the safety of final macronutrient concentrations, the form in which electrolytes are provided, and conditions or other medical treatments that may affect macro- or micronutrient needs (Table 76.10).

TABLE 76.10 Electrolytes Administered via the Total Parenteral Nutrition Solution

Suggested Electrolytes (per Day)	Conditions That May Require Alteration of Amount Provided	Electrolyte Carriers
Sodium 60-150 mEq	• Renal function • Fluid status • GI losses • Traumatic brain injury	NaCl Na acetate $NaPO_4$
Potassium 40-120 mEq	• Renal function • GI losses • Metabolic acidosis • Refeeding	KCl K acetate KPO_4
Phosphate 10-30 mM	• Renal function • Refeeding • Bone disease • Hypercalcemia • Rapid healing[a] • Hepatic function	$NaPO_4$ KPO_4
Chloride 60-120 mEq	• Renal function • GI losses (gastric) • Acid-base status	NaCl KCl
Acetate 10-40 mEq	• Renal function • GI losses (small bowel) • Acid-base status • Hepatic function	Na acetate K acetate

Suggested Electrolytes (per Day)	Conditions That May Require Alteration of Amount Provided	Electrolyte Carriers
Calcium 10-15 mEq	• Hyperparathyroidism • Malignancy • Bone disease • Immobilization • Acute pancreatitis • Renal function	Ca gluconate $CaCl_2$
Magnesium 8.1-24.3 mEq	• Renal function • Refeeding • Hypokalemia	Mg sulfate

GI, gastrointestinal.

[a]Rapid healing examples are burn and young trauma patients who have rapid tissue generation.

RFS is a severe and potentially fatal metabolic response that can occur after the reintroduction of nutrients following a period of starvation. At-risk, populations include those who have been “nothing by mouth” for 7 to 10 days or longer, those with a low BMI (<18.5 kg/m^2), or those who have experienced clinically relevant unintentional weight loss prior to admission. Patients with congestive heart failure, on mechanical ventilation, or prone to hypercapnia may also be at increased risk. RFS is characterized by electrolyte shifts due to the switch from the catabolism of fat and protein to carbohydrate metabolism, resulting in increased insulin levels and thiamine depletion. Low levels of phosphate, magnesium, and potassium are also observed. To prevent severe complications, increased monitoring while replenishing thiamine and electrolytes is recommended. The exact incidence of RFS is unknown due to varying definitions, but it is estimated that 34% to 40% of patients present with hypophosphatemia (level <0.65 mmol/L) and 4% to 10% with severe hypophosphatemia (level <0.32 mmol/L). No

clinical predictors of RFS have been identified. Therefore, it is essential to consider all critically ill patients at risk. Baseline and daily serum phosphate levels should be followed for at least 3 days or until normalized when starting EN or PN. Assessment of the risk for the development of Wernicke-Korsakoff syndrome should be considered in patients who are malnourished or with alcohol addiction with early use of aggressive intravenous thiamine replacement in those at higher risk.

In summary, all patients admitted to an ICU should undergo a nutrition assessment and nutritional risk determination upon admission and throughout their stay. Results will be used to prescribe nutrition therapy to include calculation of estimated needs, route of feeding, formulation, initiation, and monitoring, all of which should be tailored to the individual patient and altered based on the patient's changing status. Critical illness is associated with large-scale changes in macronutrient metabolism, particularly protein turnover, which increases the risk of malnutrition. Providing nutrition can favorably impact the patient's nutritional status and outcomes.

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Delivery of higher protein (average of 1.6 g/kg) compared to lower protein (average 0.9 g/kg) in almost 1,300 patients critically ill patients (~85%

SECTION XIX PROCEDURES

77 Arterial Catheterization

Daniel Reynolds

Arterial catheterization is common in intensive care medicine. Indications for placing an arterial line include direct arterial hemodynamic monitoring, frequent arterial blood gas measurements in patients with respiratory insufficiency, and less commonly, for placement of an intra-aortic balloon pump. Noninvasive arterial oxygen saturation may be inaccurate in unstable patients, and frequent direct measurement of the arterial pH, bicarbonate, and partial pressures of oxygen and carbon dioxide may be needed in patients on ventilator support or with impending respiratory collapse. In unstable patients, noninvasive blood pressure monitors may be imprecise necessitating the use of arterial lines for accurate hemodynamic monitoring.

Equipment required for catheterization includes maximal sterile barrier precautions, an intravascular catheter, suture or affixation device, noncompliant tubing, flush device with pressurized flush solution, transducer, and electronic monitoring including a connecting cable and a monitor with an amplifier and display screen. Real-time ultrasonography is recommended to increase the success rate of vessel cannulation. The tubing is connected to the transducer, which in turn is connected to the electronic monitor via a connecting cable. The noncompliant tubing transmits the pressure waveform from the artery to the transducer, which converts the pressure waveform to an electrical waveform. The electric waveform is amplified and displayed on the oscilloscope screen. The flush device allows continuous fluid infusion to prevent thrombus formation and is pressurized to prevent backup of high-pressure arterial blood into the tubing.

The most common site selected for arterial catheterization is the radial artery, followed by the femoral artery. Axillary artery

catheterization is also done, though less commonly than radial or femoral catheterization, and should be done with ultrasound. Less common sites include the dorsalis pedis and brachial arteries. Although both radial and femoral sites are acceptable, the radial site is preferred with a lower infection risk and lower risk of complications.

The radial and ulnar arteries are the distal branches of the brachial artery and are located on the lateral and medial sides of the wrists in anatomic position, respectively. They are connected by the deep and superficial palmar arches in the hand. These arterial anastomoses are taken into consideration when a radial line is placed, as a potential complication of radial artery catheterization is thrombosis. If thrombosis occurs, collateral circulation from the ulnar artery through the palmar arches typically ensures adequate blood flow to the hand. Peripheral vascular disease that occludes the palmar arches could interrupt blood flow to the hand if radial artery thrombosis occurs.

The Allen test can identify patients who have compromised collateral palmar circulation. The test is performed by raising the patient's arm to 45°, with the examiner compressing the radial and ulnar arteries with both hands. The patient is asked to repeatedly open and close the hand to drain the blood. Once pallor develops, one artery is released and the onset to palmar flushing is timed. Less than 7 seconds is considered positive, 8 to 14 seconds is equivocal, and 15 or more seconds is considered a negative test and evidence for a lack of adequate collateral circulation. The test is repeated with the other artery. Results may be difficult to interpret for patients on vasopressors and those unable to cooperate. Thus, many have abandoned the routine performance of the Allen test. An alternative measure to assess for adequate blood flow is the use of the Doppler feature on ultrasound to confirm an adequate site is chosen.

Three types of arterial catheters are commonly used. The simplest utilizes a similar angiocatheter to a peripheral intravenous (IV) without guidewire assistance. Guidewire kits offer either a preloaded system or a separate guidewire using the Seldinger technique. No method has shown superiority, and kit selection is based on provider

preference and availability. Catheter gauge and length vary based on arterial site.

Steps for Radial Artery Cannulation

1. Position the supine patient's hand with 30° to 60° of extension by propping the dorsal wrist surface on a rolled towel or other supporting structure with the ventral surface up.
2. Remove all objects from the wrist and cleanse the skin with an antiseptic solution such as chlorhexidine or Betadine.
3. Create a sterile field by draping the wrist and donning a sterile gown and gloves.
4. Use a sterile sleeve over the ultrasound probe and, utilizing the ultrasound, identify the radial artery on the lateral aspect of the wrist. Typically, a good initial site will be 3 to 4 cm proximal to the crease at the base of the thenar eminence.
5. Infiltrate a liberal volume (>2 mL) of local anesthetic after identification of the radial artery with ultrasound.
6. With the dominant hand, hold the catheter like a pencil between the first and second fingers.
7. Hold the ultrasound probe with nondominant hand, paying attention to the depth of the radial artery on the ultrasound screen. Enter the skin at a 30° to 45° angle with the catheter tip just distal to the ultrasound. Pressing too firmly with your hand or ultrasound probe can occlude flow and make cannulation difficult.
8. Advance the catheter toward the artery until a flash of blood enters the catheter tip.
9. If using a simple catheter-over-needle configuration, advance the tip of the needle slightly further into the artery to ensure that the tip of the catheter is in the arterial lumen (note: go to step 12 if using a device with a wire).
10. While holding the needle steady, advance the catheter gently forward into the artery lumen with a slight twisting motion.

11. Remove the needle; correct placement should result in pulsatile blood flow (if using a catheter without a wire, go to step 15).
12. If using a kit with a guidewire, when the flash of blood occurs, hold the needle steady, let go of the ultrasound with nondominant hand, and advance the guidewire into the arterial lumen, which should meet little resistance. Ultrasonography should document the intraluminal guidewire.
13. If using a preloaded guidewire, advance the catheter over the wire and into the arterial lumen. If using a separate guidewire, remove the needle while leaving the guidewire in place and replace it with a catheter.
14. Remove the needle and wire; correct placement should result in pulsatile blood flow.
15. Connect the catheter to the transducer tubing and flush the device.
16. Secure the catheter to the skin with suture or adhesive device.
17. Cleanse the skin and catheter with antiseptic solution and cover with sterile dressing.

Tips

If the initial attempt is unsuccessful, reposition the catheter and try again. A less steep angle may decrease the chance of traversing the artery. If further attempts are unsuccessful, try advancing the needle through the artery when the initial flash of blood is seen in the catheter tip. Next, slowly withdraw the catheter until a flash of blood again occurs and attempt to advance a guidewire through the catheter and into the arterial lumen. Once the guidewire is in place, the catheter can be advanced. Deliberate palpation of the artery, focused technique, and real-time ultrasonography will aid in a successful result. The artery often is transfixed initially with no blood flow. Thus, the catheter should always be withdrawn slowly as success can be achieved while withdrawing the catheter.

For femoral artery cannulation, a kit that utilizes a guidewire with a longer catheter is often used. The femoral artery lies in the femoral triangle bordered superiorly by the inguinal ligament, laterally by the sartorius muscle, and medially by the adductor longus muscle. From the lateral to medial positions in the triangle lie the femoral nerve, femoral artery, and femoral vein. The site should be cleaned and prepared in a sterile fashion. Similar to the radial artery, the femoral artery is identified via ultrasound and is lateral to the femoral vein (which can also be easily identified on ultrasound). Cannulation of the artery is performed in the same manner as venous cannulation. Once a flash of blood is seen in the syringe, a guidewire can be inserted through the needle which should not meet resistance. The needle can be removed and the wire can be identified in the arterial lumen via ultrasound. At this point, a femoral-length arterial catheter can be advanced over the wire into the femoral artery. The catheter should be secured to the skin with a suture of securement device, and a sterile dressing should be applied.

Complications of arterial line placement are listed in Table 77.1. Clinically significant complications are relatively uncommon but can be life-threatening. Thrombosis is the most common complication. Infection can also occur with arterial line placement. Risk can be minimized with careful sterile technique during catheter placement, routine catheter care, and radial artery preference. Importantly, risks of infection can be greatly reduced with the removal of unnecessary lines. The utility of leaving in place an arterial catheter should be discussed daily. Careful sterile technique should be used when drawing blood samples from the catheter. In part because of higher pressure blood flow, arterial lines are less likely to become infected than central venous lines. The most serious complications include bleeding and pseudoaneurysm formation, which are more common in femoral arterial catheters than radial arterial catheters. The risks of these complications can be reduced with the use of ultrasound, as well as assessments of bleeding risks including the use of anticoagulation, coagulopathy, or thrombocytopenia.

TABLE 77.1 Complications of Arterial Cannulation

Thrombosis
Local or systemic infection
Hematoma
Pseudoaneurysm (especially relevant for femoral catheters)
Hemorrhage
Significant blood loss from frequent blood testing
Heparin-induced thrombocytopenia (for heparin-flushed lines)
Retroperitoneal hematoma (femoral lines)
Limb ischemia
Peripheral neuropathy
Insertion site pain

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78 Central Venous Catheterization

Rachel K. McDonald

Central venous catheterization is commonly performed in the intensive care unit when peripheral access is inadequate. Indications for central venous catheterization include administration of noxious medications, hemodynamic monitoring, therapies requiring rapid blood flow rates (hemodialysis, plasmapheresis), insertion of invasive devices, rapid large-volume fluid or blood product administration, and emergency venous access. Noxious medications that require infusion into large central veins include vasopressors, chemotherapy, and total parenteral nutrition (TPN). Hemodynamic monitoring and invasive devices requiring central access include monitoring of central venous pressure, measurement of central venous hemoglobin saturation, and insertion of pulmonary artery catheters or transvenous pacemakers. Contraindications for central venous catheterization include known thrombosis of the target vessel and infection over the site of entry. There is no definitive cut-off for the insertion of a central venous catheter (CVC) in coagulopathic or thrombocytopenic patients; however, the subclavian site is generally avoided in coagulopathic patients due to inability to monitor for bleeding or adequately compress the site should bleeding occur. Use of a micropuncture kit or correction of the coagulopathy with fresh frozen plasma and platelet transfusion may be useful prior to the procedure.

Complications of central venous catheterization include mechanical complications (arterial puncture, pneumothorax, hemothorax, air embolus, retroperitoneal hemorrhage), infectious complications (CVC-associated bacteremia, cellulitis), and catheter-associated thrombosis or stenosis. Central-line associated bloodstream infections (CLABSIs) are associated with increased hospital mortality and health care costs. As such, the creation of

quality improvement programs designed to decrease this risk has become widespread in recent years. Although conflicting data exist, general consensus is that the risk of infection is least with subclavian cannulation and highest with femoral cannulation. Given that catheter duration is one of the biggest risk factors for CLABSI, it is noteworthy that peripherally inserted central venous catheters (PICCs) have been found to have a lower incidence of CLABSIs compared to CVCs despite PICCs being in place longer. In addition to avoiding the femoral site due to infectious complications, the Centers for Disease Control and Prevention (CDC) guidelines for cannulation site selection recommend avoiding femoral cannulation in adult patients because of increased rates of venous thrombosis and restriction of patient mobility. Subclavian cannulation should be avoided in patients with coagulopathies for the aforementioned reasons, in patients with advanced kidney disease due to the risk of subclavian stenosis, or in patients with severe hypoxemia or bullous lung disease due to the risk of pneumothorax.

The use of ultrasound guidance to aid in the placement of CVCs has been shown to decrease complication rates, decrease the number of attempts necessary to cannulate the vein, and decrease the amount of time necessary to perform the procedure. Ultrasound is used both to identify the location of the target vein and its accompanying artery and to assess the vein for thrombosis or stenosis. In general, the internal jugular vein is typically anterolateral to the carotid artery, the femoral vein is medial to the femoral artery, and the subclavian artery is superior to the subclavian vein. The vein can further be identified on ultrasound by its compressibility. Veins should be completely compressible (the anterior and posterior walls of the vessel should approximate) with pressure applied with the ultrasound probe. If the vein is not compressible, there should be suspicion for a venous thrombosis. Veins can also be identified using spectral color or pulsed wave Doppler, as flow in arteries is typically pulsatile and flow in veins is not. However, this can be misleading in certain clinical conditions, such as in patients with severe tricuspid regurgitation.

Before performing central venous catheterization, obtain informed consent based on the policies of each institution. All present must agree on the patient identification, the procedure being performed, and the site of the procedure. Sterile precautions must be observed, including hand hygiene, full sterile drape, sterile gloves, sterile gown, mask with face shield, and hair covers. All present in the room should wear masks and hair covers. It is helpful to have a nonsterile assistant present during the procedure.

The following guidelines are for the placement of central venous catheters using commercially available kits via Seldinger guidewire technique. Ultrasound guidance, if available, is preferred for completion of central venous catheterization at all locations. Typically, an out-of-plane (cross-sectional) view is used for direct guidance, except during subclavian vein catheterization when an in-plane (longitudinal) view is often used.

Internal Jugular Central Venous Catheter Placement

1. Place the patient in Trendelenburg position, and have the patient turn their head 45° to the direction opposite the site of catheter placement.
2. If ultrasound is available, use ultrasound to identify the vascular structures prior to sterilizing the procedure site. Evaluate the vein for patency and compressibility, as described, to ensure that there are no contraindications to catheterization (eg, venous thrombosis or stenosis).
3. Prepare the ultrasound for sterile use by applying sterile gel to the ultrasound transducer.
4. Don sterile gown, sterile gloves, mask with face shield, and hair cover.
5. Prepare the skin with antiseptic solution (eg, chlorhexidine or Betadine).

6. Use a sterile full-body drape with a site hole or surgical towels to cover the body, head, and face, exposing only the necessary skin.
7. Flush all ports of the catheter to ensure appropriate functioning. (If ultrasound is not available, proceed step 14.)
8. With the help of a nonsterile assistant, lower the ultrasound transducer (with sterile gel applied to the footprint of the transducer) into the sterile plastic sheath. Make sure to avoid contact between the transducer and the outer surface of the plastic sheath. The nonsterile assistant should then pull the plastic sheath to cover the length of the transducer probe that will come into contact with the sterile field.
9. Place sterile gel on the footprint of the ultrasound probe outside of the sterile sheath. Confirm location of the vessels using ultrasound again.
10. Once the site is confirmed, anesthetize the skin and subcutaneous tissue.
11. Use ultrasound to maintain a transverse view of the vein and artery. While holding the ultrasound probe over the vein with the nondominant hand, use the dominant hand to hold the introducer needle.
12. Enter the skin with the introducer needle, bevel up, just cephalad to the ultrasound transducer at a 45° angle.
13. With the ultrasound transducer, locate the tip of the introducer needle. Move the ultrasound transducer and introducer needle together in order to visualize the tip of the introducer needle throughout its approach to the target vein, aspirating while advancing. Once the vein is cannulated, dark blood will enter the syringe (Skip to step 18 if using direct ultrasound guidance.) (Figure 78.1).

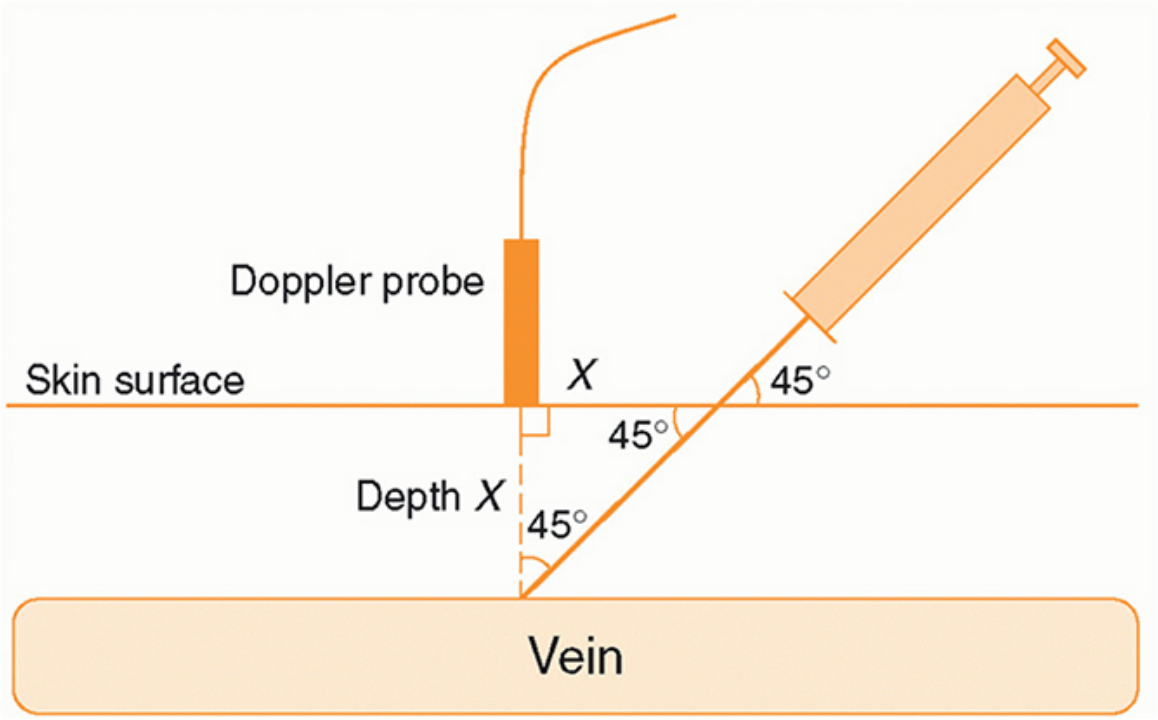


FIGURE 78.1 **Needle insertion using ultrasound guidance.** (From DeFer TM. *The Washington Manual Internship Survival Guide*. 4th ed. Wolter Kluwer Health/Lippincott Williams & Wilkins; 2013.)

14. Identify the triangle formed by the two heads of the sternocleidomastoid muscle and the sternum. Palpate the carotid pulse (Figure 78.2).

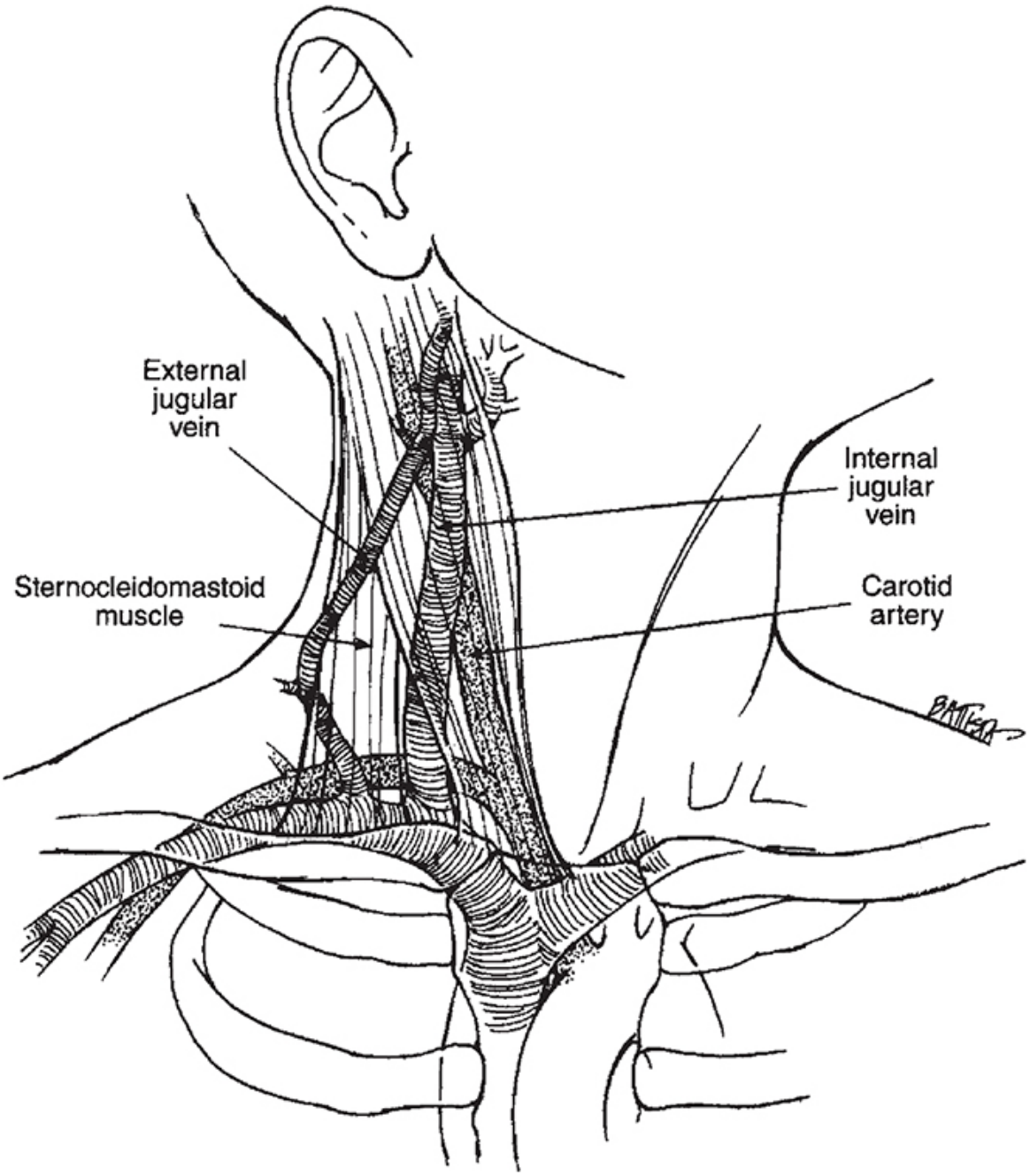


FIGURE 78.2 **Internal jugular vein anatomy.** (From Lin TL, Mohart JM, Sakurai KA. *The Washington Manual Internship Survival Guide*. 2nd ed. Lippincott Williams & Wilkins; 2001:191.)

15. Anesthetize the skin and subcutaneous tissue.
16. Palpate the carotid pulse. Lateral to the carotid pulse, advance the 22-gauge needle (finder needle), bevel up, at a 30° to 45° to

the patient, directed at the ipsilateral nipple while aspirating. If no venous blood return is noted, withdraw the needle and change the angle to a more lateral and then more medial position. Maintain palpation of the carotid pulse. When venous blood is aspirated, make note of the angle and depth of the finder needle, and remove the finder needle. *If the carotid artery is entered (bright red and/or pulsatile blood), remove the needle and hold pressure.*

17. At the same site and angle as the internal jugular vein was entered with the finder needle, insert the introducer needle until free flow of dark venous blood is noted (Figure 78.3).

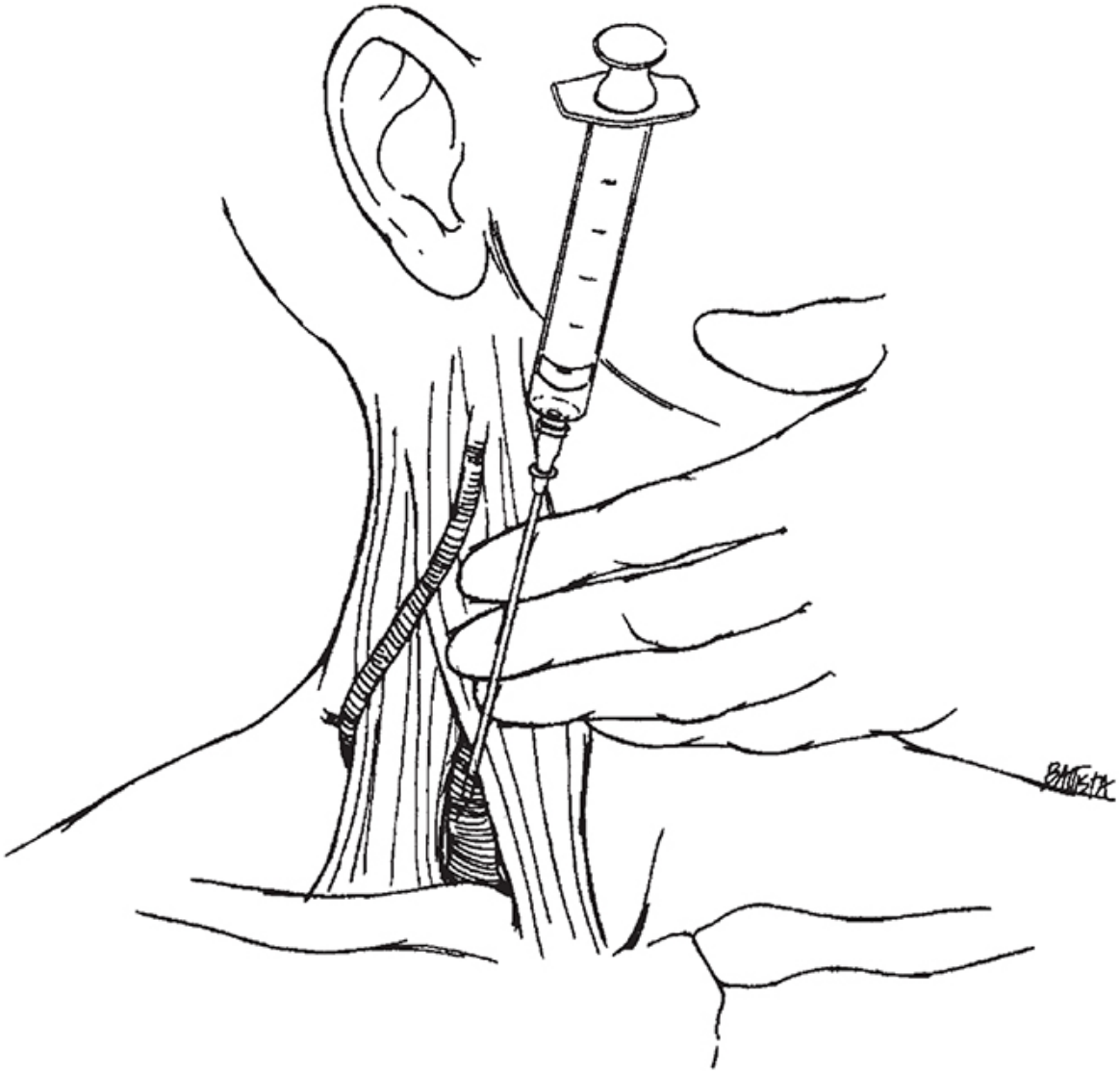
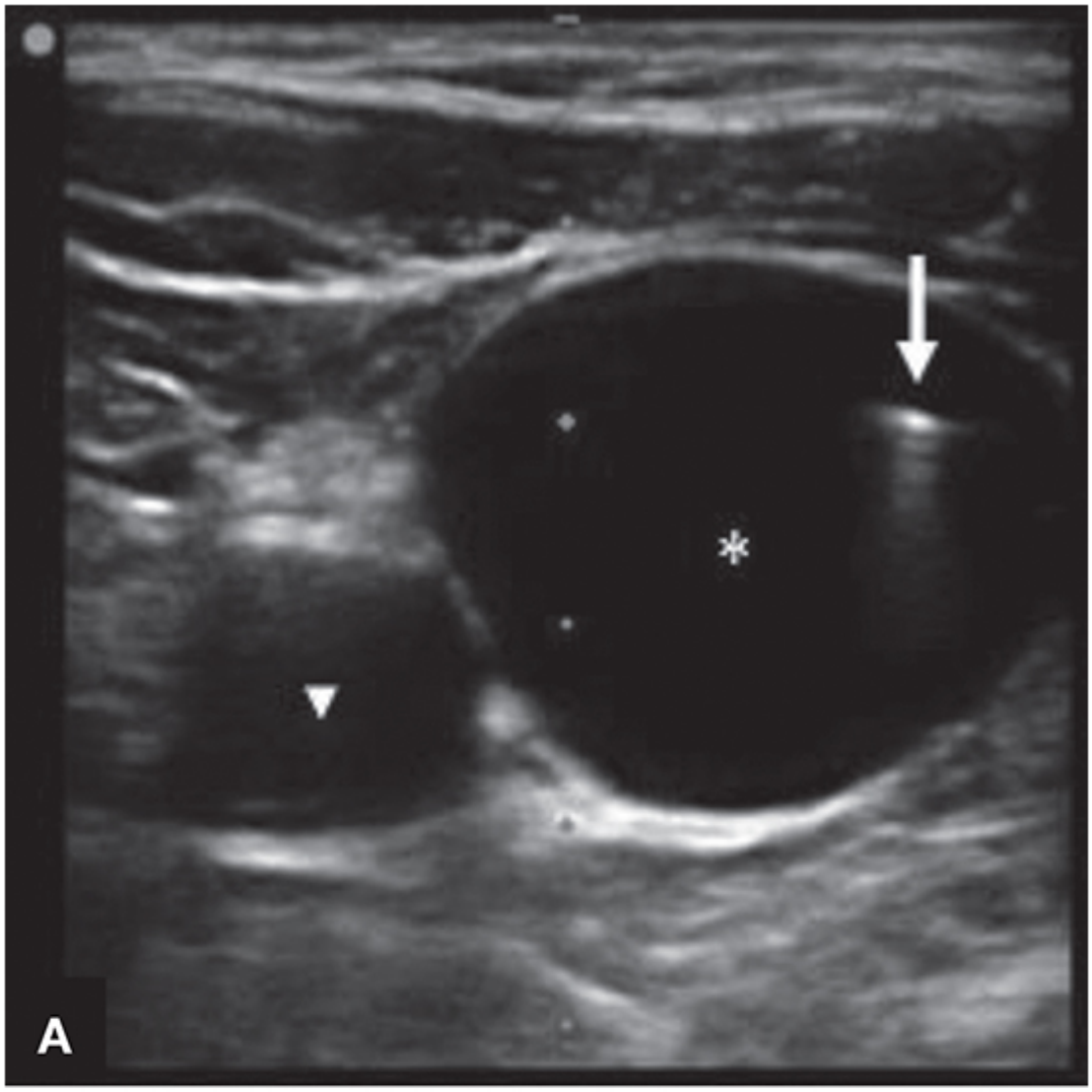


FIGURE 78.3 **Cannulation of the internal jugular vein.** (From Lin TL, Mohart JM, Sakurai KA. *The Washington Manual Internship Survival Guide*. 2nd ed. Lippincott Williams & Wilkins; 2001:192.)

18. Securely hold the needle, remove the syringe (placing a finger over the needle hub to reduce the risk of air embolism), and insert the guidewire. The guidewire should advance with little resistance. Always maintain control of the guidewire.
19. While holding the guidewire, remove the introducer needle. Once the introducer needle is outside the patient's skin, hold the guidewire at the entry site.
20. Use ultrasound to confirm correct placement of the guidewire within the lumen of the target vein. Obtain a transverse view of the internal jugular vein and identify the wire within the lumen of the vein. Trace the tract of the guidewire from the skin insertion site into the insertion into the vein. Move the ultrasound transducer in the caudal direction to follow the course of the guidewire toward the superior vena cava. Continue moving the transducer caudally confirming the guidewire remains within the lumen of the vein for its entire course through the neck. The ultrasound transducer probe can then be rotated 90° to confirm the guidewire is within the lumen of the vein in the longitudinal axis (Figure 78.4).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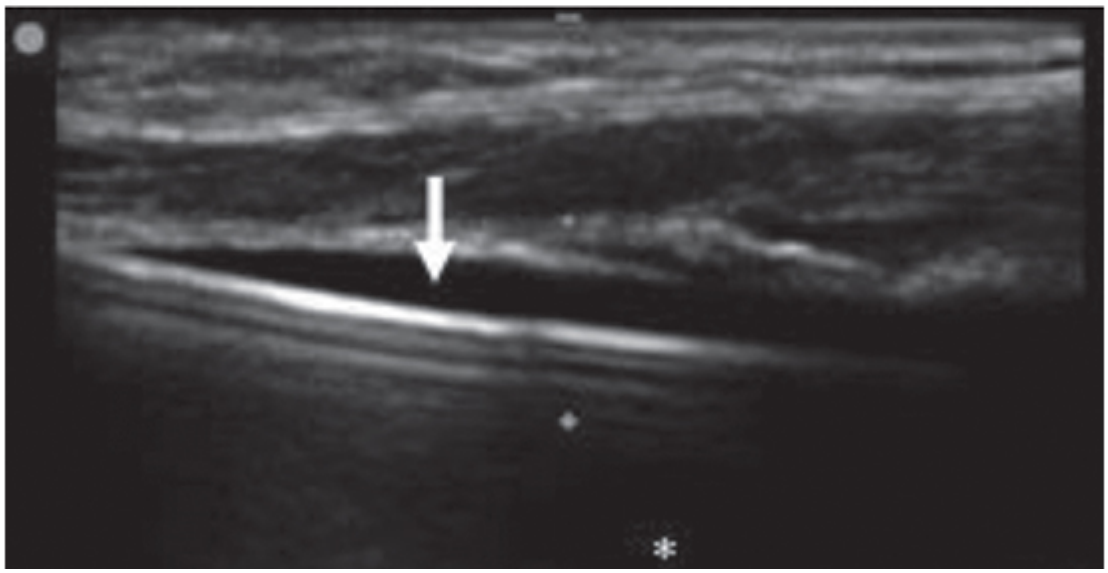


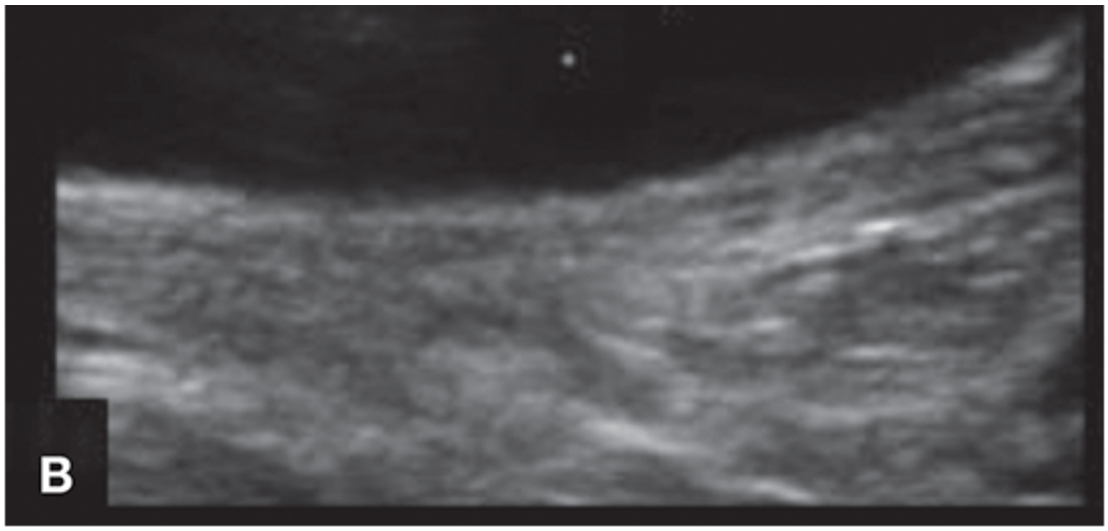


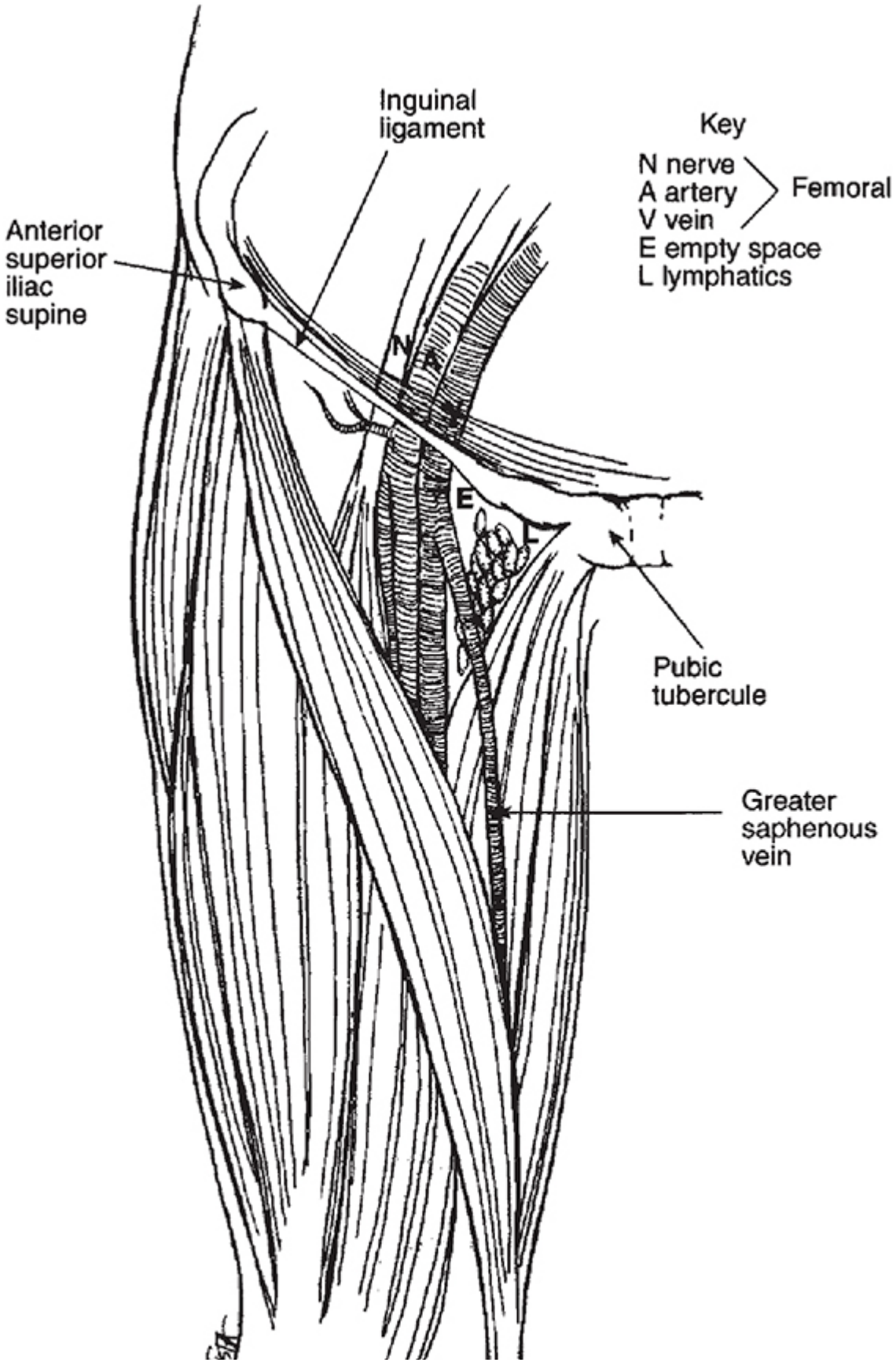
FIGURE 78.4 **Internal jugular vein with verification of guidewire placement. A**: Transverse view. **B**: Longitudinal view. Arrowhead, carotid artery; asterisk, internal jugular vein; white arrow, guidewire within internal jugular vein.

21. Using a scalpel, make a small incision in the skin at the entry site. Ensure that the cutting edge of the scalpel is facing away from the guidewire and perform a stabbing motion to make the incision.
22. Pass the dilator over the guidewire, dilate the tract to the depth of the target vein, and remove the dilator.
23. Ensure that the distal port of the catheter is open. Pass the catheter over the guidewire. When the catheter is near the entry site, feed the guidewire out until it emerges from the distal port on the catheter. Grasp the guidewire distally and insert the catheter to the desired depth (15-16 cm for the right subclavian vein, 18-20 cm for the left subclavian vein, 16-17 cm for the right IJ vein, 17-18 cm for the left IJ vein).
24. Hold the catheter in place and withdraw the guidewire. Ensure that the guidewire is intact once it is completely removed.
25. Flush all ports to ensure that they are functioning properly, and place caps on all ports.

26. Secure the catheter with suture or a commercially available sutureless kit.
27. Cleanse the site with antiseptic solution and place a sterile dressing.
28. Obtain a chest radiograph for placement and to evaluate for pneumothorax. The tip of the catheter should reside in the superior vena cava.

Femoral Central Venous Catheter Placement

1. Place the patient in the supine position with the ipsilateral thigh slightly abducted and externally rotated.
2. If using ultrasound, follow steps 2 to 13, followed by steps 18 to 27 from “Internal Jugular Central Venous Catheter Placement” section. Remember that when locating the femoral vein with ultrasound, the femoral vein typical lies medial to the femoral artery. If ultrasound is unavailable, follow steps 4 to 7 from “Internal Jugular Central Venous Catheter Placement” section, followed by the steps below.
3. Palpate the femoral arterial pulse inferior to the inguinal ligament. The femoral vein is medial to the femoral artery (Figure 78.5). With the introducer needle bevel up, enter the skin 1 cm medial to the pulse, inferior to the inguinal ligament, at a 30° to 45° (Figure 78.6). Continue to aspirate as the needle is advanced until the return of venous blood. If the needle is advanced 5 cm with no return of venous blood, withdraw while continuing to aspirate, angle more medially, and try again. *If the femoral artery is entered (bright red and/or pulsatile blood), hold pressure.*


Inguinal ligament
Key
N nerve
A artery
V vein
Femoral
E empty space
L lymphatics
Anterior superior iliac supine
N
A
V
E
L
Pubic tubercule
Greater saphenous vein

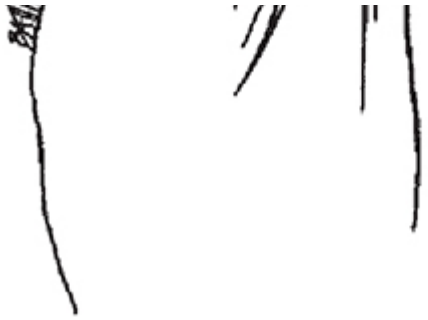


FIGURE 78.5 **Femoral vein anatomy**. (From Lin TL, Mohart JM, Sakurai KA. *The Washington Manual Internship Survival Guide*. 2nd ed. Lippincott Williams & Wilkins; 2001:183.)

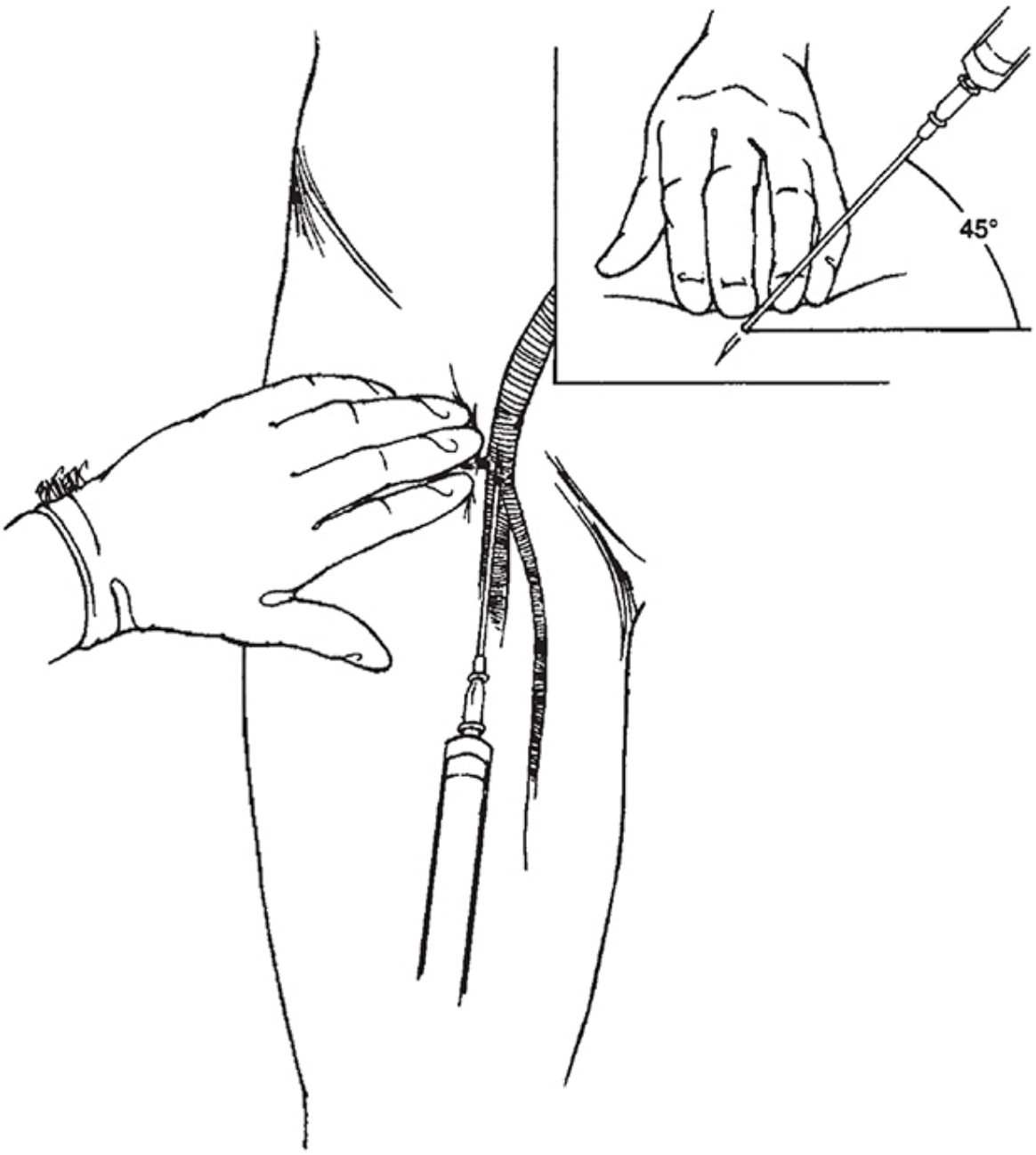


FIGURE 78.6 **Femoral vein cannulation.** (From Lin TL, Mohart JM, Sakurai KA. *The Washington Manual Internship Survival Guide*. 2nd ed. Lippincott Williams & Wilkins; 2001:197.)

4. Follow steps 18 through 27 for internal jugular central venous catheter placement. For the femoral site, the entire length of the catheter (20 cm) is inserted and secured in place.

Subclavian Central Venous Catheter Placement

1. Place the patient in Trendelenburg position. Place a towel roll between the scapulae. Keep the head in neutral position or toward the side of line placement to help direct the guidewire inferiorly.
2. Follow steps 2 to 10 from the “Internal Jugular Central Venous Catheter Placement” section for both ultrasound-guided and landmark-based approaches. Then follow steps as detailed below.
3. If using landmark-based approach, follow steps 4 to 7 below. If using ultrasound-guided approach, follow steps 8 to 13 below.
4. Place the index finger of the nondominant hand at the sternal notch and the thumb of the same hand on the clavicle where it bends over the first rib (approximately where the lateral third and medial two-thirds of the clavicle meet). The subclavian vein should traverse a line between the index finger and the thumb (Figure 78.7).

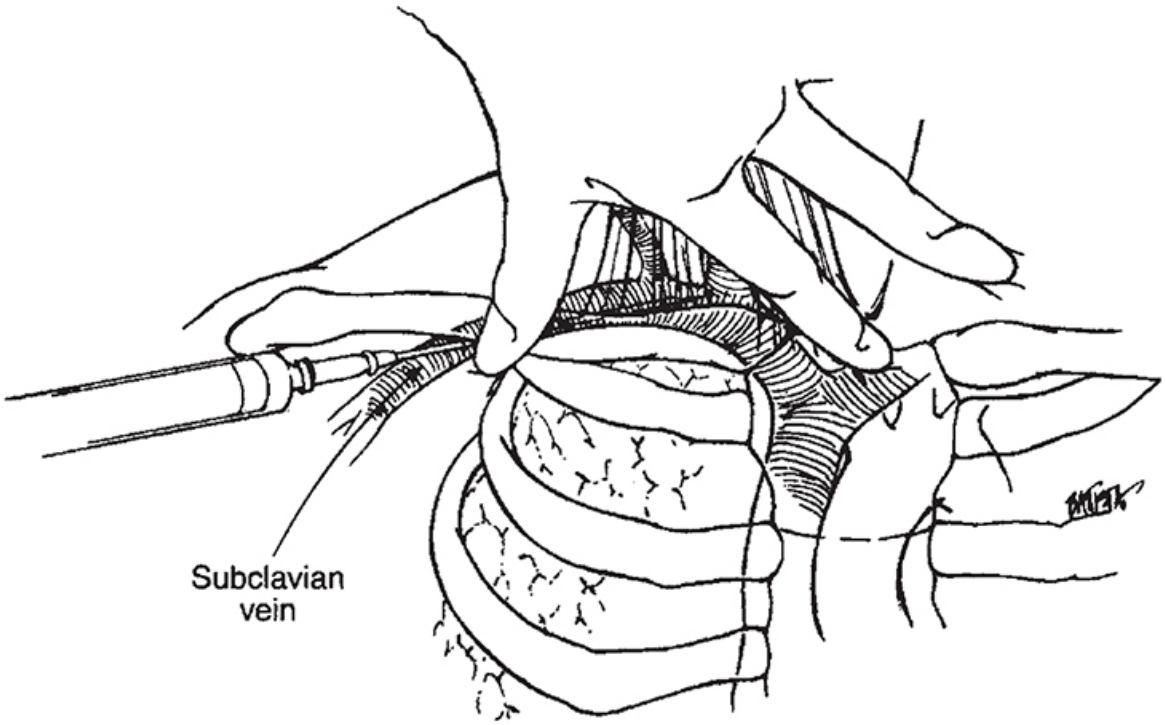


FIGURE 78.7 **Subclavian vein anatomy and cannulation.** (From Lin TL, Mohart JM, Sakurai KA. *The Washington Manual Internship Survival Guide*. 2nd ed. Lippincott Williams & Wilkins; 2001:195.)

5. Anesthetize the skin and subcutaneous tissue just inferior to the clavicle and lateral to the thumb.
6. With the introducer needle, bevel up, enter the skin lateral to the thumb and inferior to the clavicle (~2 cm inferior and 2 cm lateral to the bend in the clavicle). Aim toward the index finger (sternal notch), aspirating while advancing. It is imperative to keep the needle parallel to the floor during advancement. If the clavicle is contacted, depress the entire needle with the thumb until it passes under the clavicle, rather than changing the angle of approach. Dark blood will enter the syringe when the vein is cannulated. If there is no blood return after advancing the needle 5 cm, withdraw the needle while continuing to aspirate (frequently the vein has been pierced, and successful blood flow will be obtained during withdrawal). Redirect the needle more cephalad, and try again. Multiple repeated attempts are not recommended. Once appropriate venous return is noted, rotate the bevel of the needle 90° inferior (bevel now pointing toward the patient's feet).
7. Follow steps 18 through 28 for internal jugular central venous catheter placement.
8. Place the ultrasound probe perpendicular and inferior to the clavicle at the midportion of the clavicle (probe indicator should be directed cephalad). A portion of the ultrasound probe should overlie the clavicle.
9. Move the ultrasound probe laterally until the subclavian artery and subclavian vein are seen below the clavicle. Ensure that the subclavian vein is collapsible by applying gentle pressure with the ultrasound probe. Color Doppler can also be used to help distinguish vein from artery and assess vessel patency.
10. Enter the skin with the introducer needle, bevel up, just lateral to the ultrasound transducer at a 45°.

11. With the ultrasound transducer, locate the tip of the introducer needle. An in-plane (longitudinal) or out-of-plane (transverse) view of the vein and needle can be used.
12. If using out-of-plane ultrasound method, move the ultrasound transducer and introducer needle together in order to visualize the tip of the introducer needle throughout its approach to the target vein, aspirating while advancing. If using in-plane ultrasound method, maintain a view of the entire length of the needle as you advance the needle tip into the vein. Once the vein is cannulated, dark blood will enter the syringe. (Note: Either in-plane or out-of-plane technique is acceptable and should be chosen by proceduralist.)
13. Follow steps 18 through 28 for internal jugular central venous catheter placement.

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79 Endotracheal Intubation

Adam Anderson and Gabriel Schroeder

Endotracheal intubation maintains airway patency, assures delivery of mechanical ventilator–defined breaths, facilitates pulmonary toilet, and helps prevent aspiration. Usual indications for endotracheal intubation include airway obstruction, encephalopathy, respiratory failure, and cardiopulmonary arrest.

Risks include trauma to the oropharynx, hypoxemia from prolonged attempts, emesis with aspiration of gastric contents, unrecognized misplacement of the endotracheal tube, and death. These risks are often amplified in critically ill patients due to hemodynamic instability, severe hypoxemia, or procedural urgency. The incidence of complications increases when an inadequately trained or inexperienced provider attempts intubation. These providers should attempt to achieve adequate ventilation and oxygenation using bag valve mask devices or other airway devices that do not require visualization of the vocal cords.

Required Preparations

Assessment of the airway anatomy facilitates recognition of potentially difficult intubations. An abbreviated assessment should be performed even in emergent cases. A commonly utilized assessment tool follows the “LEMON” mnemonic (Table 79.1). Clinicians should pay particular attention to dentition and dental appliances, the mobility of the tongue and its size relative to the oropharynx or Mallampati score (Figure 79.1), range of extension and flexion of the cervical spine, mobility of the jaw, and presence of stridor. A difficult intubation may be anticipated in patients with thick necks, narrow mouth openings, prominent overbites, facial hair, large tongues, and limited motion of the

cervical spine. If available, review of prior intubation attempts may yield important information regarding airway management.

TABLE 79.1 LEMON Airway Assessment

- **L**ook externally
  - General impression of difficulty airway (anatomy, habitus, dentition, tongue, trauma, facial hair)
- **E**valuate (3-3-2 rule) patient should have at least:
  - 3 finger breadths between incisors with mouth opening
  - 3 finger breadths within the thyromental distance
  - 2 finger breadths between hyoid and thyroid cartilage
- **M**allampati Score (Figure 79.1)
  - Mallampati I and II predict easy laryngoscopy
  - Mallampati III predicts a difficult laryngoscopy
  - Mallampati IV predicts a very difficult laryngoscopy
- **O**bstruction/**o**besity
  - Supraglottic mass, secretions, blood or redundant tissue
- **N**eck mobility
  - Spinal disease or C-collar immobilization

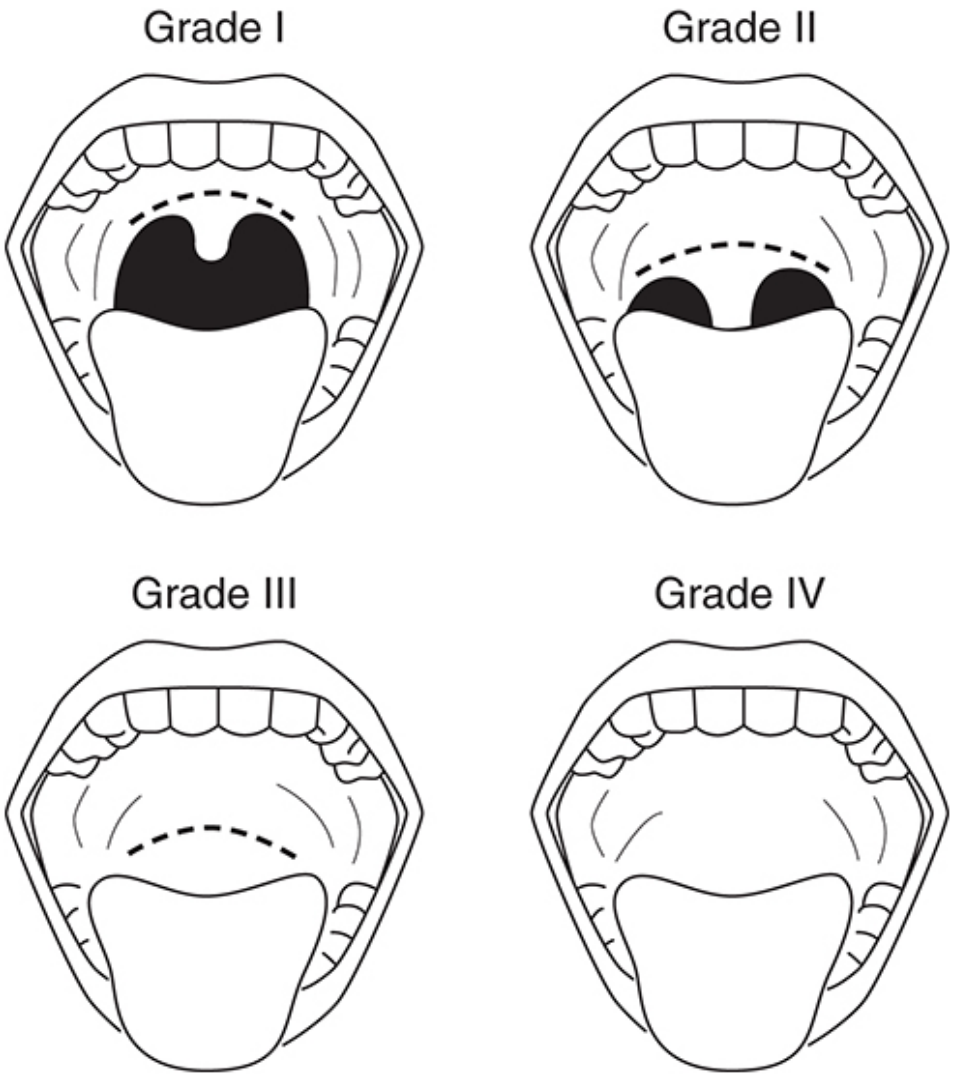

FIGURE 79.1 **Mallampati classification.** (Redrawn from Blackbourne LH. *Advanced Surgical Recall*. 2nd ed. Lippincott Williams & Wilkins; 2004. Figures 28.1-28.4.)

Successful intubation requires overcoming the normal barriers to objects entering the trachea, including reflexes arising from laryngeal stimulation, the malalignment of the major axes of the upper airway, and the anatomic barriers of the tongue and epiglottis. Endotracheal intubation is an inherently uncomfortable procedure, and even patients with decreased mental status may cough and resist attempts at intubation. In addition, laryngeal stimulation increases sympathetic tone with consequent increases in blood pressure, heart rate, and intracranial pressure.

Judicious use of appropriate medications can blunt the potential adverse physiologic effects while providing analgesia, sedation, and amnesia. Decisions regarding the use of specific agents are based on knowledge of their advantages and disadvantages relative to the patient's clinical status and comorbidities (Table 79.2). Only practitioners skilled in endotracheal intubation should administer paralytic agents. Rapid-sequence intubation (RSI) is employed when airway control is emergent, the airway is predicted to not be difficult, and gastric insufflation is contraindicated. RSI includes simultaneous administration of a paralytic and a laryngoscopy attempt prior to bag valve mask ventilation. Reliable intravenous (IV) access and vasopressors (push dose or IV infusion) should be readily available in the event of hemodynamic decompensation. Standard monitoring, including pulse oximetry, blood pressure, heart rate, and electrocardiogram (ECG), is essential prior to induction. All necessary equipment should be immediately available prior to intubation attempts. The mnemonic "STOP-MAID" can be helpful for clinicians to remember the preparations needed for emergent airway management (Table 79.3).

TABLE 79.2 Agents Used for Intubation

Agent	Action	IV Dose	Onset	Duration	Comments
Etomidate	Sedation	Stable: 0.3 mg/kg Unstable: 0.15 mg/kg	15-45 s	3-12 min	• Inhibits cortisol synthesis • Decreases focal seizure threshold

Agent	Action	IV Dose	Onset	Duration	Comments
Fentanyl	Analgesia	1-2 mcg/kg slow IV over 2 min	15 s	0.5-1 h	• Hypotension, bradycardia with large doses • Used mostly at lower doses as an adjunctive agent
Ketamine	Sedation Amnesia Analgesia	1-2 mg/kg	30 s	5-10 min	• Bronchodilator • May increase HR, BP • Use adjuvant benzodiazepine **Caution:** elevated BP or ICP
Midazolam	Sedation Amnesia	0.02-0.08 mg/kg (~1-5 mg in 70 kg adult)	30-60 s	15-30 min	• Hypotension • Beneficial in seizure
Propofol	Sedation Amnesia	Stable: 1-1.5 mg/kg Unstable: 0.5 mg/kg	30-60 s	5-10 min	• Beneficial in seizure **Contraindication:** Egg allergy **Caution:** Hypotension, bradycardia
Succinylcholine	Paralytic	1-1.5 mg/kg	30-60 s	5-15 min	**Contraindication:** Hyperkalemia, history of malignant hyperthermia, myopathy, neuropathy/stroke, severe burns

Agent	Action	IV Dose	Onset	Duration	Comments
Rocuronium	Paralytic	0.5-1 mg/kg	45-60 s	30-45 min	**Caution:** Concern for difficult intubation or bag valve mask ventilation

BP, blood pressure; HR, heart rate; ICP, intracranial pressure; IV, intravenous.

All necessary equipment should be immediately available prior to intubation attempts (Table 79.3).

TABLE 79.3 "STOP-MAID" Mnemonic

S—Suction equipment
T—Tools (laryngoscope blade, supraglottic device, bougie, oral airway, endotracheal tube stylet, and endotracheal tube—usually 7.0-8.5 for adults)
O—Oxygen (preoxygenation and apneic oxygenation)
P—Position
M—Monitoring (blood pressure, Spo_2, end-tidal CO_2, ECG)
A—Assistant, Ambu-bag with PEEP valve
I—IV access
D—Drugs (analgesic, sedative, paralytic, and vasopressor)

CO_2, carbon dioxide; ECG, electrocardiogram; IV, intravenous; PEEP, positive end–expiratory pressure; Spo_2, peripheral capillary oxygen saturation.

How to Intubate

The "sniffing" position, achieved by flexing the neck approximately 30° and extending the head at the atlanto-occipital joint to 20°, helps align the oral, laryngeal, and pharyngeal axes (Figure 79.2). Placement of towels under the occiput supports maintenance of this position. Preoxygenation is achieved using a high-flow oxygen system (15 L NC [nasal cannula] or NRB [nonrebreather mask]) for at least 3 minutes prior to induction. In the emergency room or intensive care unit (ICU) setting, preoxygenation can also be achieved with noninvasive positive pressure ventilation (NIPPV), a high-flow NC, or a tight-fitting face

mask with 10-15 L 100% oxygen. An oropharyngeal airway, nasopharyngeal airway, or jaw thrust may be required after induction to maintain upper airway patency. Apneic oxygenation via an NC should be continued during laryngoscopy to decrease the risk of desaturation.

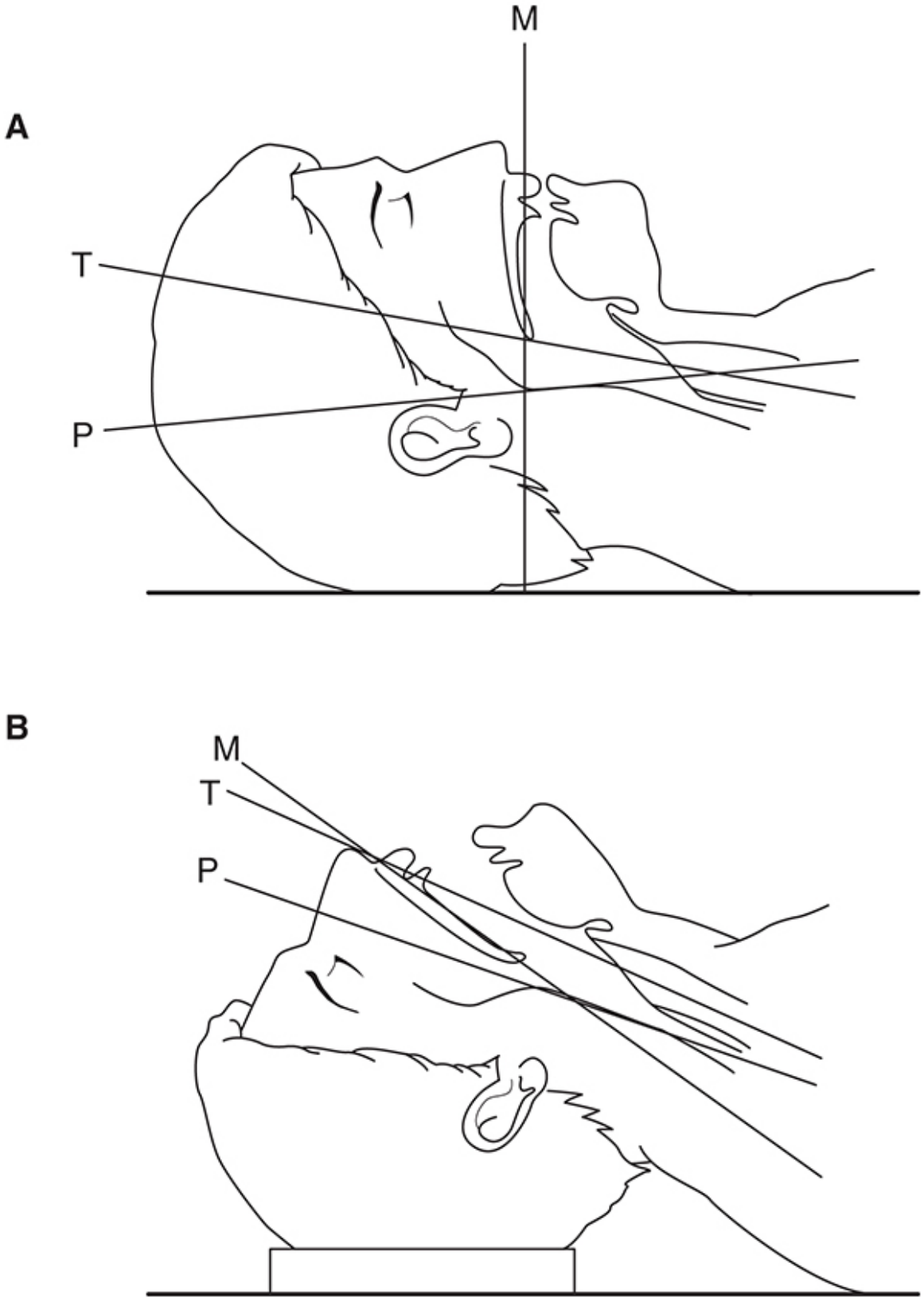
A
M
T
P
B
M
T
P

FIGURE 79.2 **Anatomic axes for endotracheal intubation. A:** With the head in the neutral position, the axis of the mouth (M), the axis of the trachea (T), and the axis of the pharynx (P) are not aligned with one another. **B:** If the head is extended at the atlanto-occipital joints, the axis of the mouth is correctly placed. If the back of the head is raised off the table with a pillow, thus flexing the cervical vertebral column, the axes of the trachea and pharynx are brought in line with the axis of the mouth. (From Snell R. *Clinical Anatomy*. 7th ed. Lippincott, Williams & Wilkins; 2003.)

The laryngoscope is used to displace the tongue and lift the epiglottis away from the glottic opening. Laryngoscope blades vary in size and shape. Blade sizes range from 0 to 4 with higher numbers corresponding to larger blades. The curved (Macintosh) blade has a broad, flat surface, and tall flange. Straight blades include Miller, Wisconsin, and Phillips. The straight blades vary with regard to their width, presence and size of flange, and shape of distal end. Curved blades apply upward traction to the base of the tongue at the vallecula, indirectly lifting the epiglottis while straight blades lift the epiglottis directly (Figures 79.3 and 79.4). The choice of specific equipment should be left to the individual practitioner. In general, straight blades allow visualization of a larger portion of the vocal cords as the epiglottis is removed from the field of view. It may be difficult to control a large tongue with a Miller blade, which is relatively narrow. While direct laryngoscopy (DL) has been the standard tool for intubation for years, video laryngoscopy (VL) may have several advantages including an increased rate of successful first-pass intubation, shorter time to successful intubation, and improved laryngeal visualization. Additionally, VL can be a powerful tool for teaching and training in airway education. Similar to DL, several shapes and sizes of VL blades are available.

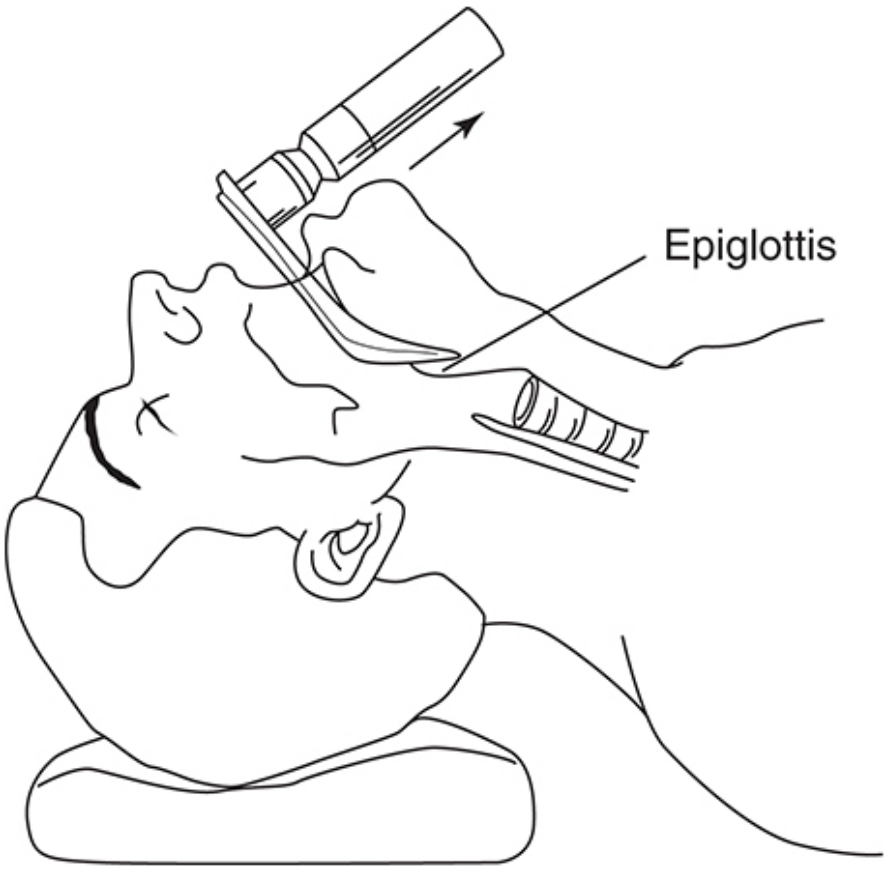

FIGURE 79.3 **Intubation with a Macintosh blade.** Blade is used anterior to the epiglottis. (From Blackbourne LH. *Advanced Surgical Recall*. 2nd ed. Lippincott Williams & Wilkins; 2004.)

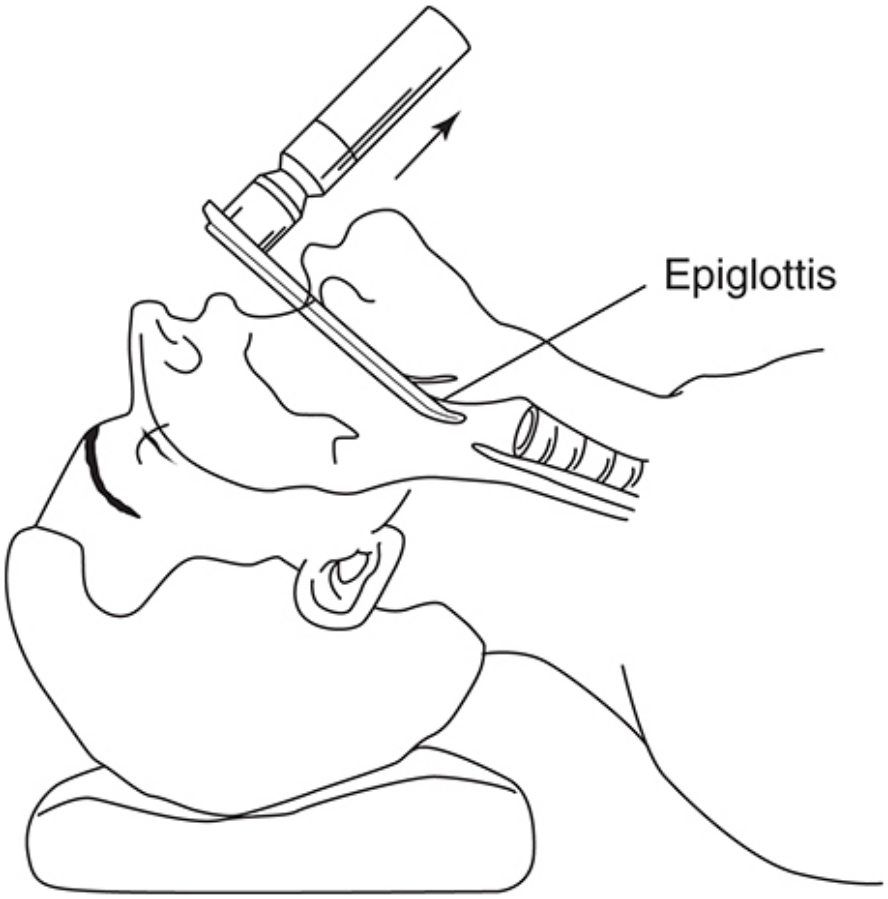

FIGURE 79.4 **Intubation with a Miller blade.** Blade is used to hold the epiglottis (posterior to the epiglottis). (From Blackbourne LH. *Advanced Surgical Recall*. 2nd ed. Lippincott Williams & Wilkins; 2004.)

As with any procedure, a verbal time-out to identify medication strategy, health care team roles, and airway algorithm is recommended. With the patient in the "sniffing" position, the laryngoscope is held in the left hand and the blade is inserted into the right side of the mouth to the base of the tongue. The blade is then moved to the midline sweeping the tongue to the left. The laryngoscope handle and blade should align with the nasal septum. The tip of straight blades is advanced to the epiglottis, while the tip of curved blades is placed in the vallecula.

The vocal cords are exposed by elevating the epiglottis through a lifting motion using the arm and shoulder in a plane 45° from the horizontal. The wrist must be kept stiff to avoid a prying motion that uses the teeth as a fulcrum. Once the vocal cords are visualized, the

endotracheal tube is advanced from the right side of the mouth with the tip directed so that it intersects the tip of the laryngoscope blade at the level of the glottis allowing the operator to view the entry of the tube into the trachea (Figure 79.5). The tube is advanced through the vocal cords until the cuff disappears. The stylet is removed and cuff inflated with sufficient air to prevent leakage during ventilation with a bag valve. The endotracheal tube must be held firmly in place at all times to prevent displacement. Attempts at intubation should take no longer than 1 minute. In patients where there is difficulty intubating the trachea, repeated attempts increase the risk of trauma and hypoxemia. A tracheal tube introducer, or bougie, can be used in patients with suboptimal laryngoscopic views. A bougie can be particularly useful when the epiglottis is seen, but the cords cannot be visualized. Lastly, a supraglottic airway device can be placed as a temporary airway to provide adequate oxygenation and ventilation while a more skilled provider is contacted for assistance.

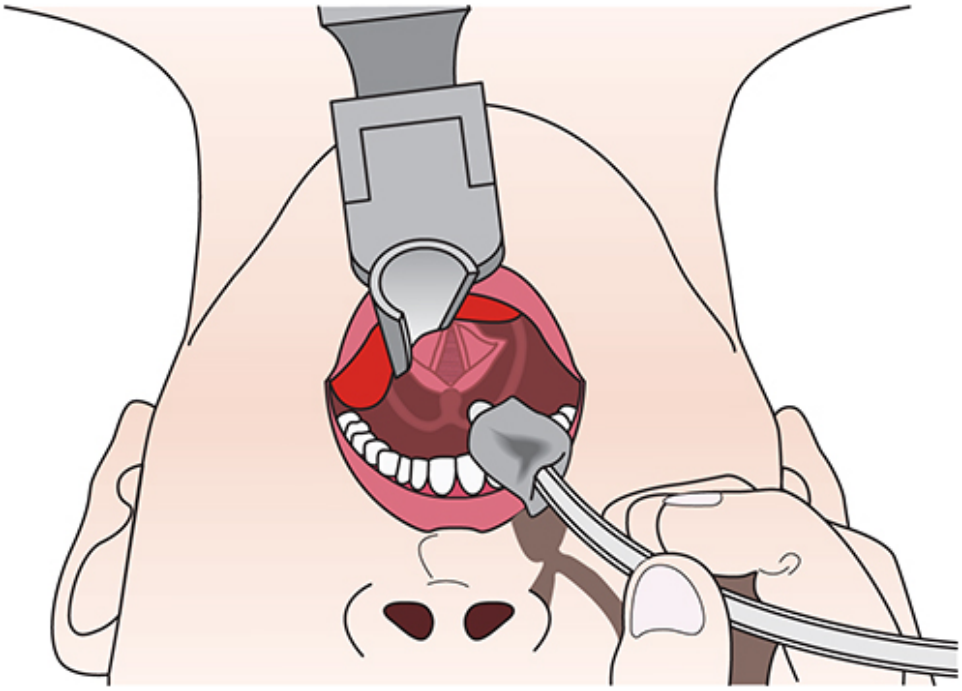

FIGURE 79.5 **Endotracheal intubation/intubating**. Illustration showing correct method for intubating victim during endotracheal intubation. (From *LifeART Image* copyright © 2007 Lippincott Williams & Wilkins. All rights reserved.)

Additional Techniques

Cricoid pressure (Sellick maneuver) may decrease the risk of aspiration by compressing the esophagus between the cricoid cartilage and the vertebral column. Pressure should be applied prior to intubation attempts and maintained until confirmation of correct endotracheal tube placement. Bimanual laryngoscopy using the right hand to manipulate the thyroid cartilage or hyoid bone may improve visualization of the vocal cords. An assistant must apply identical pressure to facilitate optimal visualization. Alternatively, the “BURP” (backward, upward, rightward pressure) maneuver can be employed, though typically with less success than bimanual laryngoscopy.

Especially when a difficult airway is anticipated, alternate approaches to endotracheal intubation via DL include VL, optical stylets, supraglottic airways, laryngeal tube airways, fiber-optic intubation, and percutaneous tracheostomy. Supraglottic and laryngeal tube airways are placed blindly into the upper airway and form a seal over the laryngeal inlet to ventilate and oxygenate patients while partially occluding the esophagus allowing for directed ventilation into the trachea.

Confirmation

Correct tube placement is established via visualization of the endotracheal tube through the vocal cords, condensation within the endotracheal tube, visualization of chest expansion, and auscultation over the epigastrium and lung fields during ventilation. Continuous end-tidal carbon dioxide (CO_2) confirmation is preferred, although colorimetric end-tidal CO_2 detection devices may be used. A chest radiograph should be reviewed to document appropriate endotracheal tube placement.

Upon confirmation of placement, the endotracheal tube is secured firmly in place with either tape or a commercial device. Initial ventilator management is an integral component of any airway and should not be overlooked, especially if paralytics were administered. Regardless of

the outcome, a debriefing session for feedback from team members is recommended to improve future attempts.

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80 Percutaneous Tracheostomy

Brandt Lydon, Nathan Moulton, and Alexander C. Chen

Tracheostomy is a technique for creating an artificial airway between the neck surface and cervical trachea. There are two main tracheostomy techniques: the surgical approach, which involves surgical dissection to form the tract between the neck surface and the trachea, and the more recent percutaneous approach. Variations of the percutaneous approach use the Seldinger technique to form the tract between the neck surface and the trachea. Although not suitable for all patients, the percutaneous approach offers potential advantages over the surgical approach, particularly in appropriately selected intensive care unit (ICU) patients. A meta-analysis showed a lower rate of peristomal bleeding and postoperative infection with percutaneous tracheostomy. In addition, because percutaneous tracheostomies are commonly performed in the patient's ICU room, the risks of adverse events associated with transporting patients who are critically ill are reduced, and scheduling flexibility is increased. Lastly, some research also supports percutaneous tracheostomies as a more cost-effective tracheostomy approach for ICU patients.

The remainder of this chapter will focus on percutaneous tracheostomies.

Indications

1. Upper airway obstruction: A surgical approach is often more appropriate for upper airway obstruction due to tumor.
2. Need for long-term mechanical ventilation
3. Access for frequent suctioning and other airway care

4. Treatment of severe obstructive sleep apnea when continuous positive airway pressure is ineffective or not tolerated

Contraindications

Contraindications unique to the percutaneous approach include difficult-to-palpate neck anatomy or a history of prior neck surgery or radiation. Patients with high ventilatory and oxygenation requirements may be better served by a surgical approach because of the reduced ability to ventilate around the bronchoscope and a higher likelihood of greater positive end–expiratory pressure loss during the procedure. Coagulopathies should be corrected prior to proceeding, although there are no well-validated thresholds. One center described a low rate of complications for percutaneous tracheostomy in the setting of significant thrombocytopenia as long as platelets were administered before the procedure. Hypotension can be worsened because of the significant amount of sedatives commonly needed to perform the procedure, making hypovolemia and hypotension relative contraindications.

Timing of Tracheostomy Procedure in Patients Who Are Critically Ill

Most patients receive tracheostomies in the ICU because of difficulties in weaning from the ventilator or because they cannot protect and clear their own airways. Potential advantages of tracheostomy over prolonged endotracheal intubation include greater comfort, decreased sedation requirements, enhanced ability to participate in rehabilitation, and facilitated weaning. Optimal timing for tracheostomy in ICU patients is controversial. If prolonged intubation is predicted at admission, a tracheostomy on day 1 or 2 may be appropriate. In most patients, tracheostomy is considered after 1 to 2 weeks of endotracheal intubation. The preponderance of

evidence supports early tracheostomy over prolonged endotracheal intubation. A recent meta-analysis, including 12 studies, suggested that early tracheostomy is associated with more ventilator-free days, shorter ICU stays, decreased sedation requirements, and improved long-term mortality when compared to late tracheostomy.

Considerations in Patients Tested Positive for COVID-19

The COVID-19 pandemic posed unique challenges for performing percutaneous tracheostomy, primarily due to the fact that it is an aerosol-generating procedure. There is a lack of data guiding the timing of tracheostomy in patients who are critically ill with COVID-19, but initial cohort studies and a joint consensus statement from the American College of Chest Physicians (ACCP)/American Association of Bronchology and Interventional Pulmonology (AABIP)/Association of Interventional Pulmonology Program Directors (AIPPD) suggest taking an approach similar to non–COVID patients with hypoxic respiratory failure and meeting indications for tracheostomy. Techniques to minimize aerosolization (including periods of apnea during aerosolizing procedure steps and using modified bronchoscopic guidance with endotracheal intubation throughout the procedure) are being studied. However, if aerosolization is considered to be a significant risk, open surgical tracheostomy may be preferred. Teams performing percutaneous tracheostomy should minimize personnel in the room to only those necessary for the procedure, and full personal protective equipment (PPE) should be worn (including an N-95 respirator, eye protection, and gown/gloves/hand hygiene).

Procedure for Percutaneous Tracheostomy

Approaches differ slightly on the basis of operator preferences and the particular brand of percutaneous tracheostomy kit used. The following description outlines the Ciaglia technique modified by the use of a single dilator with a hydrophilic coating.

1. Explain procedure, including risks and benefits. Obtain consent.
2. A team approach makes the procedure more efficient and optimizes patient safety. The bronchoscopist is responsible for bronchoscopic guidance and maintenance of the airway. The bronchoscopist should be skilled in airway management in case of accidental extubation during the procedure. Video bronchoscopy is advantageous because it allows the operator to see the interior of the trachea continuously during the procedure. The nurse assists with intravenous anesthesia during the procedure. A respiratory therapist makes appropriate changes to the ventilator throughout the procedure. The operator performs the procedure and communicates to other members of the team to ensure coordination.
3. Increase F_{IO_2} to 100%.
4. Monitor blood pressure every 3 to 5 minutes; monitor other variables, including heart rate, pulse oximetry, and airway pressure, continuously.
5. A variety of anesthetic regimens can be used, although combinations of a benzodiazepine and short-acting narcotic or propofol work well. Traditionally, after deep sedation is achieved, a paralytic is administered to prevent coughing. Currently, we perform most of our procedures without a paralytic and have not had significant problems with this approach.
6. A small pad is placed under the shoulders to slightly extend the neck. The neck is prepared with chlorhexidine, and a large surgical drape is used to completely cover the patient, with a small opening at the neck. The operator scrubs and dons a hat, protective eyewear, a mask, and sterile gloves and gown.

7. The operator selects the appropriate incision site by palpating the thyroid and cricoid cartilages and the sternal notch. Typically, the space between the first and second cartilaginous rings or the second and third cartilaginous rings can be approached, with an incision halfway between the cricoid cartilage and the sternal notch.
8. After creating a skin wheal with lidocaine, the needle is raised to form a 90-degree angle with the trachea. The tract is anesthetized, and the needle is advanced slowly while continuously aspirating. Air bubbles will appear when the needle penetrates the trachea.
9. A 1.5- to 2-cm incision through the skin and superficial subcutaneous tissue is made either horizontally or vertically.
10. A small, curved Kelley clamp is used to dissect a tract down to the trachea.
11. The bronchoscopist carefully withdraws the endotracheal tube over the bronchoscope, until the tip lies just below the vocal cords and the tracheal lumen is visible. Firm pressure is applied to the trachea with the Kelly clamp to confirm placement between the appropriate cartilaginous rings.
12. Under continuous bronchoscopic visualization, the catheter-over-needle apparatus is advanced through the skin incision, between the selected tracheal rings, and into the trachea under continuous bronchoscopic surveillance. The catheter is advanced off the needle into the trachea while the needle is withdrawn.
13. The guidewire is threaded through the catheter toward the carina.
14. The catheter is removed, leaving the guidewire in place.
15. The bronchoscopist verifies the integrity of the posterior membrane and ensures proper guidewire placement.
16. A punch dilator is advanced through the trachea and then removed.
17. Next, the curved dilator is inserted over the wire into the trachea. The dilator is then removed.

18. Tracheostomy tube is loaded onto the dilator and advanced over the guidewire. Percutaneous tracheostomy tubes have tapered ends that allow for easier tracheal insertion.
19. Next, the bronchoscopist removes the bronchoscope from the endotracheal tube and quickly inspects through the tracheostomy tube to ensure proper placement. The patient is reconnected to mechanical ventilation through the tracheostomy tube.
20. The bronchoscopist can inspect the trachea above the tracheostomy tube to rule out active bleeding, suction blood and secretions, confirm the tracheostomy balloon is completely in the airway, and then remove the endotracheal tube.
21. The tracheostomy tube is sewn into place, secured with tracheostomy ties, and dressed appropriately.
22. The tracheostomy tube is changed on day 10 to 14.

Complications

Percutaneous tracheostomy complications are typically divided into early and late categories. More common early complications include transient hypotension and minor bleeding during the procedure. While massive hemorrhage from damage to the innominate vessels has been described, it is exceedingly rare. Pneumothoraces and cardiac arrests are uncommon early complications. Fractured tracheal rings occur frequently, although the clinical significance of this complication is unknown. Late complications include stomal infections, bleeding, accidental decannulation, and tracheal stenosis. Bronchoscopic visualization reduces, though does not eliminate, older described complications such as posterior tracheal perforation. There is growing evidence, including limited randomized controlled trials (RCTs), suggesting ultrasound guidance may play a role in decreasing the rate of injury to anterior neck structures, decreasing the number of attempts at cannulation of the airway, and leading to more frequent midline placement.

Tracheal stenosis rates vary widely in the literature, with some reports finding them to be rare, while others suggest them to be more common in patients undergoing percutaneous tracheostomies compared with those who undergo surgical tracheostomies.

The use of different techniques and study population selection may explain some of the discrepancies in the literature. When stenosis develops in patients who have undergone percutaneous tracheostomy, it tend to be subglottic in location and may be more challenging to correct surgically.

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81 Chest Tube Insertion

Tej M. Patel and Praveen Raju Chenna

Definition

Thoracostomy refers to the insertion of a hollow, flexible tube into the pleural space.

Indications

1. Drainage of air or fluid from the pleural space
2. Administration of therapeutic pleural agents such as fibrinolytic agents or sclerosants.

Contraindications

1. Bleeding diatheses (prothrombin time or partial thromboplastin time >2 times normal, platelets <50,000, or creatinine level >6) should be corrected in nonemergent settings.
2. A history of thoracic surgery or pleurodesis on the side of proposed chest tube insertion requires additional caution, as lung tissue can become adherent to the chest wall after these procedures, resulting in lung injury or hemorrhage during insertion. Image guidance or operating room placement may be required.

Imaging

Confirmation of the suspected pleural process prior to tube placement is imperative to avoid inadvertent damage to the lung or other organs and the attendant morbidity and mortality. In patients with cystic or emphysematous lung disease, large bullae can mimic pneumothoraces on standard upright chest radiographs. Tumors with associated atelectasis can be mistaken for pleural effusions. In the postoperative setting, diaphragmatic paralysis or injury with resultant diaphragmatic elevation on routine chest radiographs may be confused with a significant pleural effusion. Attempted chest tube placement can cause significant morbidity in these situations. Lateral decubitus films may help confirm the existence of free-flowing air or fluid. If any doubt exists, or in difficult cases, chest computed tomography or ultrasound imaging should be performed.

Site Selection

1. Physical examination findings consistent with a pleural effusion include decreased breath sounds on auscultation, dullness to percussion, loss of tactile fremitus, and asymmetric chest wall expansion with inspiration. Physical examination findings consistent with pneumothoraces include hyperresonance and decreased breath sounds. In tension pneumothoraces, hemodynamic instability, specifically hypotension and tachycardia, may be observed.
2. For free-flowing air or fluid, chest tubes are traditionally placed in the “Triangle of Safety,” delineated by the lateral border of the pectoris major or anterior axillary line (anteriorly), the lateral border of the latissimus dorsi or middle axillary line (posteriorly), and the fifth intercostal space (inferiorly). Alternatively, the second interspace in the midclavicular line can be used for drainage of pneumothoraces with small, percutaneous catheters.
3. Loculated air or fluid collections often require image guidance by ultrasound or fluoroscopy for optimal tube placement. A good understanding of the overlying anatomy is required in this

situation to prevent damage to anatomic structures during tube insertion.

4. Avoid any overlying cutaneous abnormalities such as cellulitis, candidiasis, burns, or other wounds.

Choosing the Optimal Tube Size and Approach

The blunt dissection and guidewire (also known as Seldinger) methods are the two most commonly used techniques for tube thoracostomy (Table 81.1). Different indications dictate the appropriate tube size and approach (see Chapter 17, Pleural Disorders in the Intensive Care Unit, for more information on pleural disorders and indications for chest tube insertion). Chest tube sizes are reported in French (F), where 3F equals 1 millimeter (mm) of outer diameter, so that 24F tube equals 8 mm.

TABLE 81.1 Chest Tube Size and Insertion Method by Indication

Indications	Tube Size	Insertion Method
Simple pneumothorax—including primary, secondary, traumatic, and iatrogenic	8-14F	Image-assisted guidewire
Loculated pneumothorax	8-14F	Image-assisted guidewire
Pneumothorax—positive pressure ventilation	20-28F	Either image-assisted guidewire OR blunt dissection
Bronchopleural fistula	≥28F	Blunt dissection
Malignant effusion	8-14F	Image-assisted guidewire

Indications	Tube Size	Insertion Method
Complicated parapneumonic Effusion—pH <7.2[a]	8-14F ≥20F	Image-assisted guidewire Either image-assisted guidewire OR blunt dissection
Empyema[a]	8-14F ≥20F	Image-assisted guidewire Either image-assisted guidewire OR blunt dissection
Hemothorax	>32F	Blunt dissection

[a]Based on clinical situation and expertise with available procedures.

Traditionally, large-bore chest tubes (LBCTs) greater than 20F were used for most pleural diseases requiring drainage. Increasing data suggest that small-bore chest tubes (SBCTs), sized 8 to 14F, are less painful and easier to place with few complications. It is well established that SBCTs are equally as efficacious in pneumothoraces (primary, secondary, traumatic, and iatrogenic) and malignant pleural effusions. Recent data suggest that these smaller caliber chest tubes (14F) may be equally as effective as larger bore chest tubes (28-32F) for managing infected pleural spaces and hemothoraces. For hemothoraces specifically, recent data demonstrates that SBCTs are equally as efficacious as LBCTs, as evidenced by similar rates of treatment failure, duration of chest tube placement, and hospital length of stays.

As such, there is now considerable practice variation in determining the appropriate chest tube size for any given clinical scenario and pleural disorder. Traditional indications for LBCTs have included bronchopleural fistulae, pneumothorax in mechanically ventilated patients, and hemothorax due to theoretical risk that an SBCT may not be sufficient for adequate drainage.

Anatomically, free-flowing air will accumulate anteriorly and apically in the supine position; therefore, chest tubes placed for

simple pneumothoraces are typically placed in an anteroapical direction. In contrast, fluid accumulates in the posterior and basal diaphragmatic gutters, and, as such, chest tubes placed for effusions are placed in an inferoposterior direction. Loculated air or fluid collections are often more readily approached by real-time, image-guided approach as location of air or fluid is more variable.

PROCEDURE STEPS

Blunt Dissection Approach

1. Explain benefits, risks, and alternatives. Obtain consent.
2. Gather necessary equipment (Table 81.2). Kits prepared ahead of time can simplify this process.
3. Typically, the patient is placed in a semirecumbent position with the head and shoulders about 30° off the bed. The ipsilateral arm is placed above the head for exposure of the axilla and to increase the distance between ribs.
4. Clean the area with antiseptic and sterilely drape.
5. After appropriate site and corresponding inferior rib identification, infiltrate subcutaneous tissue with 1% lidocaine without epinephrine (Table 81.1).

TABLE 81.2 Materials Necessary for Blunt Dissection Thoracostomy

Sterile Gloves	60-mL Syringe	Kelly Clamps × 2
Mask	25-G needle[b]	Sterile dressing
Antiseptic solution[a]	22-G × 1.5-in needle[c]	Silk sutures
Sterile drape or towels	Scalpel with no. 11 blade	Sterile specimen cups

Sterile Gloves	60-mL Syringe	Kelly Clamps × 2
1% Lidocaine w/o epinephrine (50-mL bottle)	Chest tube	Pleural drainage system
10-mL syringe	Sterile gauze	

[a]Chlorhexidine or Betadine.

[b]To anesthetize skin.

[c]To anesthetize tract and pleura.

a. Next, inject lidocaine down to the appropriate rib. Move needle superiorly, over the rib in a stepwise fashion, aspirating as you advance, stopping to inject lidocaine every 1 to 2 mm.
b. Confirm entry into the pleural space with aspiration of air for pneumothoraces or fluid for effusions by aspirating the syringe as it is advanced.
c. Next, withdraw the syringe while aspirating until no air or fluid return and inject lidocaine to generously anesthetize the parietal pleura. Typically, the equivalent of 25 to 40 mL of 1% lidocaine should achieve adequate local anesthesia. Maximum dose of lidocaine used should not exceed 4.5 mg/kg.

6. Make a skin incision through the subcutaneous tissue that is wide enough to insert a finger (1-2 cm).
7. Using medium-sized Kelly clamps, bluntly dissect to the top of the selected rib. This is done by applying forward pressure with the clamps while opening, relaxing forward pressure while closing, and repeating as necessary. Once the rib is reached, continue with blunt dissection over the top of the rib. A rush of air or fluid signals entry into the pleural space. When entering the pleural space, use caution not push too far, so as to prevent lung injury.
8. Place finger through tract into the pleural space, sweep circumferentially around the entry site to confirm the lack of adherent lung in the direction of chest tube placement.

9. Clamp the end of the chest tube with a Kelly clamp and guide into the pleural space. Direction is generally anteroapical for drainage of air and inferoposterior for drainage of fluid. Depending on body wall size, insert to 8 to 12 cm at the skin.
10. Attach external end of tube to the drainage system. Drainage of air or fluid as well as evidence of respiratory variation suggest proper placement into the pleural space.
11. Securely suture tube to prevent dislodgment. Some operators place a mattress suture at the time of the insertion, leaving the ends loose, which they use to close the incision at the time of tube removal.
12. Using occlusive gauze to seal the skin around the tube is controversial. Some authors argue that this leads to skin breakdown.
13. Dress area with a generous amount of gauze and tape.
14. Check chest x-ray for proper placement.
15. Check on chest tube output, signs of respiratory variation, and the presence of air leaks at least daily. Evaluate site for bleeding or signs of infection.

Guidewire Approach

Note: This approach may vary slightly depending on kit used.

1. Obtain consent and position patient. Obtain materials as per Table 81.2 and the guidewire insertion kit and prepare area as for blunt dissection approach. Multiple companies make preassembled kits containing most of the necessary materials; check kit labeling to ensure all materials are available.
2. Anesthetize rib and pleural space in the selected interspace using same technique described earlier.
3. Insert the introducer needle just superior to the appropriate rib. Stop just past the point where fluid or air is aspirated.
4. Remove syringe and cover needle opening with finger to prevent excessive air entry. Introduce guidewire into pleural space.

Remove needle from patient, leaving guidewire in pleural space.

5. Make a small skin nick at the wire entry site to allow introduction of dilators and chest tube.
6. Using sequential dilators, dilate tract into pleural space. Generally, tactile feedback is present when the dilator has punctured through the parietal pleura (can be described as a giving way or “pop”). Dilators should be advanced only a small amount (1 cm) beyond this point to ensure proper tract formation, while using caution to avoid further advancement as that may potentially harm the lung.
7. Introduce chest tube over the wire into the pleural space. Confirm that all openings are in the pleural space (depending on body wall size, typically at 8-12 cm at the skin). Remove guidewire.
8. Connect chest tube to drainage system.
9. Suture tube in place and dress with gauze and tape as mentioned earlier.
10. Check chest x-ray for proper placement.

Drainage Systems

The most common drainage system for hospitalized patient is the three-bottle drainage system. The functions of the three-bottle system are most commonly incorporated into one container today. The first column serves as a drainage repository, collecting fluid that drains from the pleural space. The second column serves as a water seal, which prevents retrograde air entry into the pleural space. The third column allows for adjustment of the negative pressure applied to the pleural space.

Guidelines for Chest Tube Removal

There is considerable practice variation involved in chest tube removal. The most important requirement is for the resolution of the initial indication for placement. For pneumothoraces, this generally means a fully expanded lung with resolution of the air leak, and for pleural fluid, this implies a maximum drainage of 100 to 150 mL/d. There is no consensus regarding timing of pulling during respiratory cycle, nor regarding the practice of tube clamping, placing on water seal, or continuing suction until removal.

Our approach is to remove the chest tube from suction, that is, place on water seal once the indication for placement has resolved. We then perform a follow-up chest x-ray 12 to 24 hours later. If there is no significant air leak or reaccumulation of air or fluid, the tube can be considered for removal. Additionally, the tube can be clamped for 2 to 4 hours, with careful monitoring and a repeat chest x-ray to confirm stability prior to chest tube removal.

REMOVAL STEPS

1. Gather materials—suture removal kit, gauze, 1.0 silk suture, needle driver, scissors, 10-mL 1% lidocaine without epi, 10-mL syringe with 25-G needle, tape.
2. Patients can be given a small amount of narcotic prior to removal where clinically indicated.
3. Remove sutures.
4. Have patient make a full inspiration and pull tube out quickly while occluding the track with gauze in your other hand.
5. Approximate the wound.
    a. For LBCT: Approximate the incision either by tying a previously placed mattress suture or by placing new suture.
    b. For SBCT: A simple occlusive dressing should suffice.
6. A follow-up chest x-ray should be taken 12 to 24 hours later (or sooner, if clinically indicated) to rule out recurrence of pneumothorax or pleural fluid.

Complications

Complications from chest tube placement are less well-studied than complications associated with other common thoracic procedures. The site of placement (emergency department, intensive care unit, floor, or operating room) and circumstances of placement (emergent or nonemergent) are undoubtedly important. One study looked at complications from chest tubes inserted by pulmonary fellows with attending supervision. Many, although not all, of the patients were in the intensive care unit. The largest number of chest tube placements in the study were for ventilator-associated or iatrogenic pneumothoraces. Problems were stratified as early (first 24 hours) or late and by size of the chest tube placed (≤14F or larger). Early complications included the tube not being placed in the pleural space, nonfunctional tubes, and laceration of the lung. Late complications included nonfunctional tubes, site of infection, and a leak around tube. All complications were more common with small tubes (36%) versus larger tubes (9%).

Other possible complications include hemothoraces from intercostal vessel injury or intra-abdominal placement. Infections associated with tube placement are uncommon. Prophylactic antibiotic use is supported by one meta-analysis in trauma patients, but is probably not justified in other clinical situations.

SUGGESTED READINGS

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82 Paracentesis

Rachel K. McDonald

Paracentesis is a frequently performed procedure in the intensive care unit for both diagnostic and therapeutic purposes. Diagnostic paracentesis should be performed in patients with suspected spontaneous bacterial peritonitis (SBP) or ascites of unknown cause. In patients with significant shortness of breath or abdominal discomfort, therapeutic paracentesis can alleviate symptoms. Complications of paracentesis are rare and usually without clinical consequence. Ascitic fluid leaks may occur if a large-bore needle is used, a large skin incision is made, or if a Z-track technique is not performed. A repeat paracentesis to relieve tension in the abdomen may be required to control ascitic fluid leak if the ascitic fluid cannot be decreased with diuretic treatment. Although perforation can occur if the needle punctures the bowel wall, it rarely results in clinically significant secondary peritonitis. Bleeding due to inadvertent puncturing of an artery or vein is an uncommon complication, but can be potentially fatal. Selecting a paracentesis site that avoids the inferior epigastric vessels decreases the risk of bleeding. The risk of bleeding may also be increased in patients with renal disease. Treatment is usually supportive and rarely requires further intervention.

Many patients undergoing paracentesis (especially those with underlying liver disease) are coagulopathic and thrombocytopenic at the time of the procedure. It has been shown in such patients that there is no need to correct the coagulopathy or transfuse platelets prior to the procedure. Paracentesis should not be performed in patients with disseminated intravascular coagulation. Additionally, in patients with small bowel obstruction, a nasogastric tube should be placed prior to the procedure. In patients who have undergone prior abdominal surgery, the area of the surgical scar should be avoided,

as this may be associated with bowel tethering to the abdominal wall by adhesions. Patients with urinary retention should undergo bladder catheterization prior to paracentesis.

The most common sites of paracentesis are the abdominal left lower quadrant, suprapubic, or right lower quadrant regions. Physical examination, particularly percussion and examining for shifting dullness, can help determine the procedure site. In addition to physical examination findings, bedside ultrasound should be performed when available to help identify the ideal procedure site and improve the overall safety of the procedure. This will ensure adequate intraperitoneal fluid is present for safe sampling, will help avoid abdominal organs, and will allow for the use of color Doppler or power color Doppler to identify abdominal wall vasculature and mitigate the risk of bleeding.

The indications for the procedure, as well as its risks and benefits, should be discussed with the patient, and informed consent should be obtained. Once the site of the procedure has been determined and all present agree on the identification of the patient, the site, and the procedure being performed, one can proceed with paracentesis.

Performance of Paracentesis

Note: Ultrasound Assistance, if Available, Is the Preferred Method

1. Use ultrasound to identify a site with ascitic fluid and an absence of bowel, solid organs, or abdominal wall vasculature. Mark the site with a pen or make an indentation in the skin (usually with the syringe tip).
2. Wear sterile gloves and a mask with a face shield at a minimum. Use additional sterile equipment according to hospital policy.
3. Place the patient supine with the head of the bed slightly elevated.

4. Prepare the site with an antiseptic solution (eg, chlorhexidine or Betadine), and place a sterile drape.
5. Inject local anesthesia (1% lidocaine) using a 22- or 25-gauge needle. Start with a subcutaneous wheel followed by deeper anesthesia. Maintain continuous negative pressure on the syringe while injecting the deeper tissues, injecting lidocaine periodically. Maintain an angle of entry similar to the angle of the ultrasound probe used during site selection.
6. Once ascitic fluid is obtained, inject lidocaine around the peritoneum.
7. Make a small incision at the insertion site with a scalpel to facilitate insertion of the paracentesis catheter.
8. Ideally, use a needle designed for paracentesis (eg, Caldwell needle), though a large-bore intravenous catheter may suffice. Attach a 10-mL syringe to the needle.
9. Use the Z-tract technique by pulling the skin 2 cm caudad prior to inserting the needle. This theoretically causes the tract to close, thus reducing the rate of leakage when the catheter is withdrawn.
10. Insert the needle slowly, with continued negative pressure on the syringe. When obtaining ascitic fluid, stop advancing the needle/catheter system, advance the catheter over the needle, and remove the needle.
11. Obtain an adequate amount of ascitic fluid for diagnostic studies (typically at least 25 mL). Inoculate culture bottles at the bedside to increase yield.
12. If performing therapeutic paracentesis, connect tubing from the catheter to the vacuum bottle.

Diagnostic Considerations

Diagnostic studies performed on ascitic fluid are determined by the clinical situation (Table 82.1). Other less common diagnostic studies include triglycerides (chylous ascites), amylase (pancreatic ascites),

mycobacterial culture (tuberculous ascites), and bilirubin (bile leak). If there is concern for SBP, fluid should be sent for cell count and culture. A cell count demonstrating more than 250 polymorphonuclear cells/mm^3 without secondary source of infection (eg, perforated viscous) or a grossly bloody tap suggests SBP. The definitive diagnosis is based on positive culture results. In patients with findings suggestive or diagnostic of SBP, empiric treatment should be initiated with a third-generation cephalosporin (ceftriaxone or cefotaxime) or a fluoroquinolone (ciprofloxacin or levofloxacin) pending culture results and sensitivities.

TABLE 82.1 Common Clinical Situations and Pertinent Studies for Ascitic Fluid

Clinical Situation	Studies	Comments
Concern for SBP	• Cell count • Culture (blood culture bottles inoculated at bedside)	• >250 cells/mm^3 consistent with SBP • Culture definitive for diagnosis • Treat with third-generation cephalosporin or fluoroquinolone.
Determining if ascites is secondary to portal hypertension	• Serum albumin • Ascites albumin • Total protein	• SAAG ≥1.1 g/dL (portal hypertension): cirrhosis, alcohol hepatitis, cardiac ascites, portal vein thrombosis, Budd-Chiari syndrome, liver metastases. TP ≥2.5 g/dL: cardiac ascites. TP <2.5 g/dL: cirrhotic ascites • SAAG <1.1 g/dL: peritoneal carcinomatosis, tuberculous peritonitis, pancreatic ascites, nephrotic syndrome, serositis

Clinical Situation	Studies	Comments
Concern for malignant ascites	• Cytology	• Sensitivity can be increased by sending three samples and examining samples promptly.

SAAG, serum ascites albumin gradient = (serum albumin) − (ascites albumin); SBP, spontaneous bacterial peritonitis; TP, total protein.

The routine use of albumin infusion (6-8 g albumin/L fluid removed) after large-volume paracentesis (5 L or more) is controversial but has been shown to decrease circulatory dysfunction and the potential precipitation of hepatorenal syndrome.

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83 Lumbar Puncture

Jennifer Alexander-Brett

The lumbar puncture (LP) is commonly performed in the intensive care unit to obtain cerebrospinal fluid (CSF) for diagnostic purposes. This chapter will discuss the indications, technique, complications, and common pitfalls of performing an LP in adults.

Indications and Contraindications

It is useful to remember the old adage, "If you consider an LP, you should do it." Delay in the diagnosis of meningitis leads to inappropriate treatment and difficulty in later establishing the diagnosis when the patient fails to improve. Likewise, prompt diagnosis of subarachnoid hemorrhage results in early treatment of aneurysms and prevention of rebleeding. Table 83.1 lists common indications for LP.

TABLE 83.1 Common Indications for Lumbar Puncture

- Diagnosis of bacterial, viral, fungal, parasitic, or mycobacterial meningitis
- Diagnosis of carcinomatosis meningitis
- Diagnosis of subarachnoid hemorrhage
- Assessing central nervous system and meningeal inflammation for diagnosis of conditions, including multiple sclerosis, Devic disease, and neurosarcoidosis
- Measuring CSF protein levels for the diagnosis of Guillain-Barré syndrome
- Measuring intracranial pressure for diagnosis of pseudotumorcerebri
- Removing CSF for treatment of pseudotumorcerebri or normal-pressure hydrocephalus

CSF, cerebrospinal fluid.

There are few contraindications to LP. Coagulopathy is an important contraindication because an LP may cause an epidural hematoma leading to compression of the cauda equina. No studies have established useful cutoffs, but an international normalized ratio greater than 1.4, partial thromboplastin time greater than 50, and/or platelet count less than 100,000/mm^3 are commonly corrected with fresh frozen plasma and/or platelet transfusions prior to an LP. Those targets can be lowered in the setting of hematologic disorders and thrombocytopenia resistant to correction, and the risk-to-benefit should be assessed individually. In the setting of altered mental status, papilledema, focal neurologic deficit, or if there is suspicion for subarachnoid hemorrhage, a head computed tomography scan should be obtained prior to LP. Signs of herniation and large posterior fossa masses preclude an LP because the pressure drop following CSF removal can precipitate tonsillar herniation.

Other contraindications to LP include local skin infections, known spinal cord tumors, and very recent surgical instrumentation. Prior to performing an LP, informed consent must be obtained according to the policy of each institution.

Technique

COLLECT THE SUPPLIES

Gather the following: a sterile 20-gauge or smaller spinal needle with a stylet, a sterile 25-gauge needle and syringe for local anesthesia, topical antiseptic, sterile drape and gauze, 1% to 2% lidocaine solution, a sterile manometer, sterile surgical gloves, and tubes for collection of the fluid. With more experience, a smaller gauge spinal needle, preferably a Sprotte needle, helps reduce post-LP headaches. In patients with morbid obesity, a needle longer than the standard 3.5-in needle may be necessary.

POSITION THE PATIENT

Lateral decubitus positioning is required to accurately measure the intracranial CSF pressure. The patient is positioned so that the hips and shoulders align above one another, the back is parallel to the wall, and the patient is curled up with the knees and chin tucked deeply into the torso (Figure 83.1). In other cases, a sitting position aids in determining the midline of the spine, increasing the space between spinous processes, and possibly enhancing filling of the lumbar cistern, thus improving the chance of a successful LP. In this position, the patient is positioned such that the back is straight and arched outward, with the chin tucked deeply into the chest. Ultimately, the choice of positioning should be determined by the indications for the LP, patient comfort and/or ability to cooperate, and the operator experience.

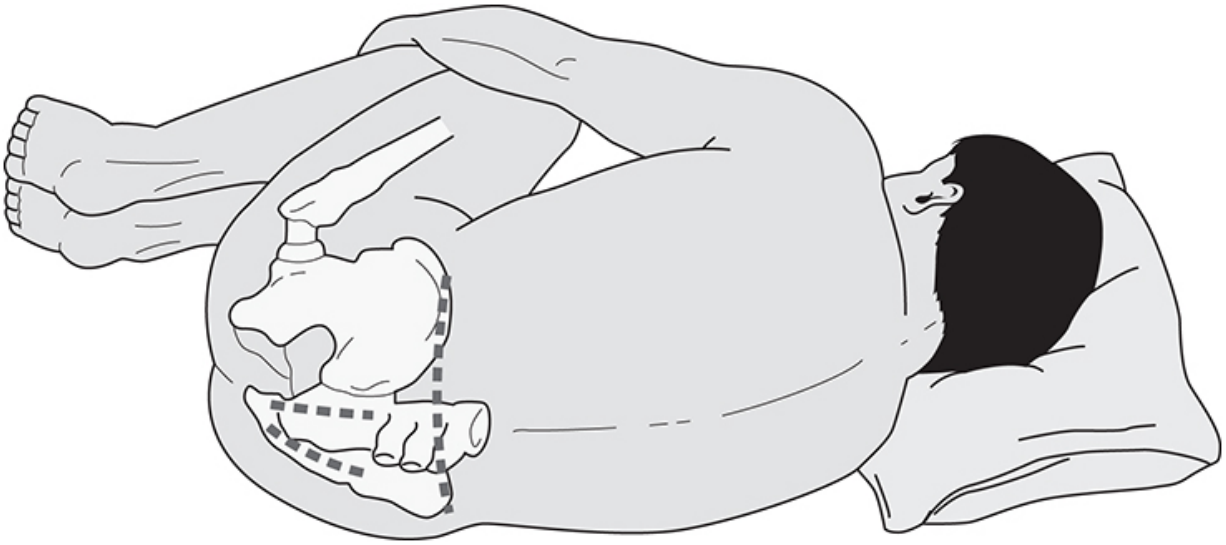

FIGURE 83.1 **Positioning the patient.** Tuffier line is indicated by the dashed line. (From Taylor C, Lillis CA, LeMone P. *Fundamentals of Nursing*. 2nd ed. JB Lippincott; 1993:543, with permission.)

FIND THE L4-5 SPACE

In most adults, the spinal cord ends at L1, although in a few adults, it may end at L2. Therefore, the L3-4, L4-5, and L5-S1 spaces represent safe and effective locations for inserting a spinal needle. In

most adults, a line (Tuffier line, Figure 83.1) drawn across the tops of both iliac crests crosses either the L4 spinous process or the L4-5 space. Use the spinous space on or immediately below the Tuffier line. Attention to superficial anatomy helps ensure the appropriate placement of the spinal needle.

SCRUB AND ANESTHETIZE THE SPACE

Scrub the location with an antiseptic solution. Betadine has historically been the preferred antiseptic agent due to concerns about possible neurologic side effects related to chlorhexidine use. However, there are now adequate data indicating that chlorhexidine is a safe alternative to Betadine and does not significantly increase the risk of neurologic complications. Using sterile gloves, place a sterile drape at the selected location with the lumbar space above it exposed. Lidocaine is injected subcutaneously and to a depth of about 2 cm along the expected track of the spinal needle.

INSERT THE SPINAL NEEDLE

The spinal needle, with its stylet in place, should then be inserted through the skin along a tract angled toward the navel or about 15° cephalad. The needle must be entered at midline and orthogonal to the plane of the back. The bevel should initially be perpendicular to the long axis of the body to minimize tearing of the dura and the subsequent post-LP headaches.

ADVANCE THE SPINAL NEEDLE

After penetrating the skin and subcutaneous fat, the needle should traverse the supraspinous ligament, the interspinous ligaments, the ligamentum flavum, the epidural space, and finally the dura (Figure 83.2). Severe pain may indicate being away from the midline. Once the needle has been inserted about 3 to 4 cm, or if a “pop” or sudden loss of resistance is experienced, remove the stylet to check for CSF. If no CSF is obtained, replace the stylet and advance the needle another 2 to 3 mm before removing the stylet again to check

for CSF. Once the lumbar cistern has been entered, CSF should flow freely through the spinal needle, and the stylet can be replaced to limit CSF leakage until it can be collected or a manometer can be attached to measure CSF pressure. Hitting bone while inserting the needle indicates either incorrect angling of the needle or entry away from the midline. When this occurs, retract the needle to the subcutaneous tissue, reposition its angle to be closer to 15° or less cephalad and directed more toward the midline, and then reinsert. This procedure can be repeated a few times until a tract free of bone is achieved. After several attempts at the first lumbar space, using the L3-4 space (the space immediately above the Tuffier line) is permissible, but using any higher spaces risks inserting the needle into the tip of the spinal cord.

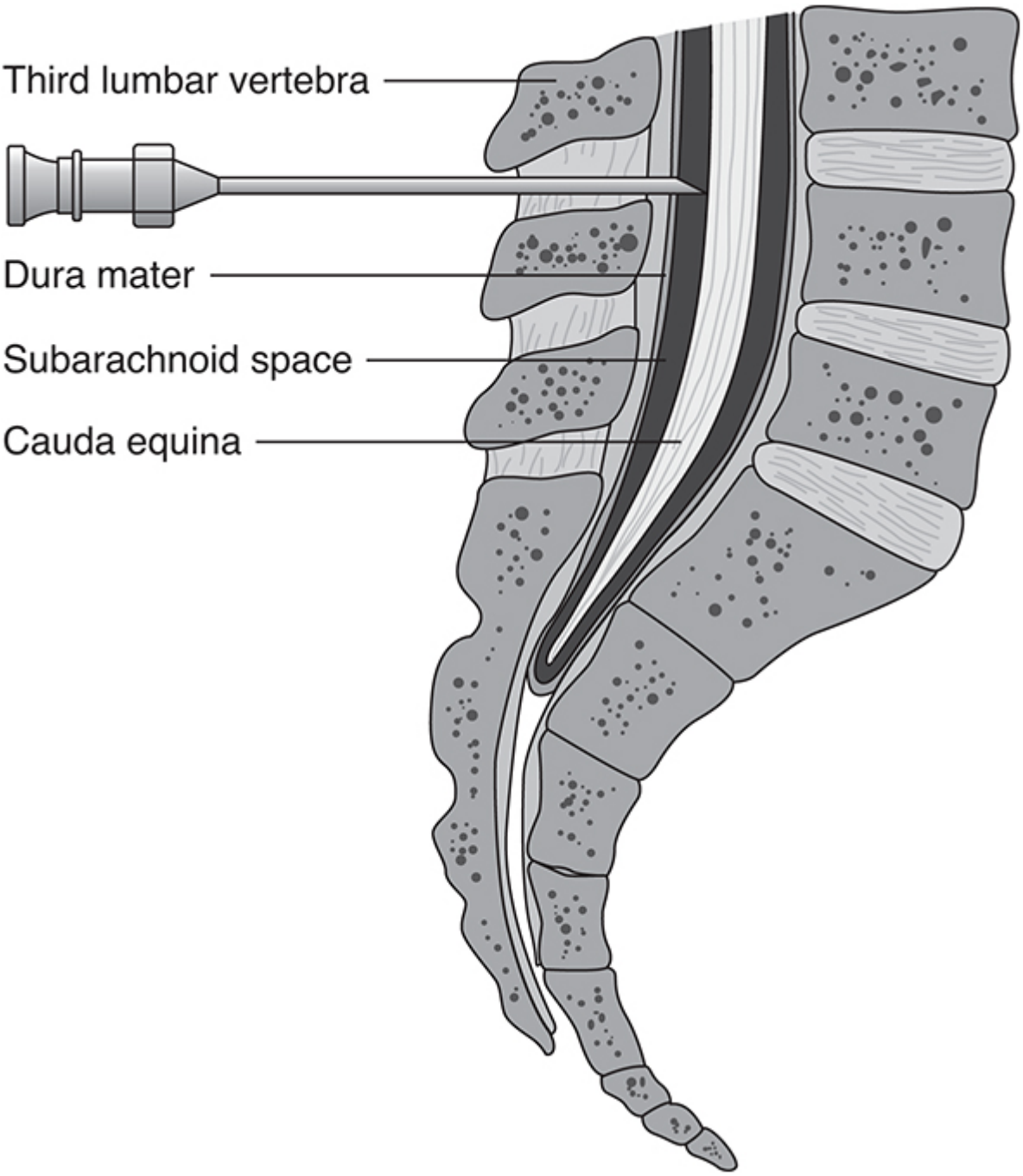

FIGURE 83.2 **The ideal tract of the spinal needle.** (From Taylor C, Lillis CA, LeMone P. *Fundamentals of Nursing*. 2nd ed. JB Lippincott; 1993:543, with permission.)

On occasion, the LP needle is inserted to the hub without obtaining CSF. This problem can be avoided by using a needle that is sufficiently long, ensuring a correct entry point and angle, and

occasionally by sitting up the patient. Point of care ultrasound guidance may increase the success of a bedside procedure when identification of landmarks is challenging. Ultrasound can also aid selection of the appropriate length spinal needle by measuring the skin-ligamentum flavum distance using a low-frequency curvilinear transducer with deep tissue penetration. Fluoroscopic LP guidance may be required in the setting of lumbar spinal surgery/hardware, scoliosis, or severe degenerative disease.

MEASURE CEREBROSPINAL FLUID PRESSURE AND COLLECT FLUID

Once the needle has entered the lumbar cistern, a manometer can be used to measure the "opening" CSF pressure. This measurement is accurate only when the patient is in the lateral decubitus position and relaxed enough to allow visible respiratory excursions of the CSF in the manometer. Normal pressure is 8 to 22 cm H_2O, although it can be slightly higher in normal patients who are obese or in patients on positive pressure ventilation. The fluid in the manometer should be collected for CSF analysis. Sufficient CSF should be collected for all of the necessary tests, and additional fluid should be collected and saved in case further testing is desired. If the opening pressure is less than 20 cm H_2O, the minimum amount of fluid necessary should be collected. Fluid analyses are listed in Table 83.2. If the CSF appears bloody initially and later it clears, this suggests a "traumatic" tap, whereby the needle had punctured a vein en route to the lumbar cistern. Xanthochromia, or a yellowish tint to the fluid, indicates either blood products greater than 12 to 24 hours old in the subarachnoid space or greatly elevated protein levels. Careful replacement of the stylet before and after collection helps avoid excessive CSF leak. After CSF collection, a closing pressure can be measured if necessary. Replace the stylet before removing the needle. Samples collected should be sent for cell count with differential, chemistry, and Gram stain/culture; additional studies may be included based on the suspected underlying diagnosis (Table 83.2). Of note, samples should be analyzed as soon as

possible after collection, as cell counts are prone to decline markedly over the course of hours.

TABLE 83.2 Common Tests for CSF Analysis (To Be Ordered Based on Clinical Concern)

- Complete cell count and differential
- CSF glucose and protein levels
- Gram stain and bacterial, fungal, and mycobacterial cultures
- Cytology and wet mount inspection
- Spectrophotometer analysis for xanthochromia
- IgG and albumin levels, serum-IgG and serum-albumin levels to determine the IgG index: (CSF-IgG/CSF-albumin)/(serum-IgG/serum-albumin)
- Oligoclonal bands
- PCR tests for a variety of pathogens, including HSV, VZV, EBV, CMV, enteroviruses, TB, arboviruses, JC virus, and toxoplasmosis
- Other tests for pathogens, including cryptococcal antigen testing, syphilis (VDRL or FTA-ABS), cysticercosis, histoplasmosis, coccidioidomycosis, and malaria

CMV, cytomegalovirus; EBV, Epstein-Barr virus; FTA-ABS, fluorescent treponemal antibody-absorption; HSV, herpes simplex virus; IgG, immunoglobulin G; PCR, polymerase chain reaction; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory; VZV, varicella-zoster virus.

Complications

Following the LP procedure, the patient should be placed in the supine position for 1 hour. This helps reduce post-dural puncture headaches immediately after an LP, though probably does not prevent post-LP headaches due to a dural tear and persistent CSF leakage. The latter can be reduced by appropriate spinal needle selection and proper technique. Fluids, caffeine, acetaminophen, and nonsteroidal anti-inflammatory drugs are effective in most cases of post-LP headaches. Characteristically, the headache worsens with

sitting up or standing and resolves when lying down. If the headaches persist longer than 5 days, an epidural blood patch may be required.

Rarely, the patient may complain of paresthesias or pain referred to one leg. During the procedure, this indicates impingement of a nerve root, and the spinal needle should be retracted, repositioned further toward the midline, and then reinserted. Careful controlled insertion of the needle helps avoid such nerve damage. When symptoms of cord compression occur following the procedure, there is concern for an intraspinal epidermoid tumor or an epidural hematoma. In both cases, obtaining a magnetic resonance image or computed tomography is mandatory, and neurosurgical consultation is warranted if any such mass is discovered.

Other rare complications include cerebral herniation syndromes and spontaneous rupture of a subarachnoid arterial aneurysm. These can be avoided by careful physical examination and, when indicated, brain imaging prior to the LP.

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This comprehensive article reviews the relevant anatomy for performing a lumber puncture. It is well written and is advised particularly when one is having trouble successfully performing the procedure.

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A video and accompanying article that demonstrates the proper method of performing a lumber puncture. This is highly recommended to everyone who has never performed this procedure before.

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An article providing detailed description of the proper method for performing lumber puncture under ultrasound guidance.

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84 Thoracentesis

Lauren Sattler and Praveen Raju Chenna

Definition

Thoracentesis—insertion of a needle and/or catheter into the pleural space for aspiration of air or fluid.

Indications

1. To evaluate pleural effusions of unknown etiology
2. To exclude empyema or complicated parapneumonic effusions in febrile patients with pleural effusions
3. Therapeutic removal of air or fluid from the pleural space

Relative Contraindications

1. Uncooperative or agitated patient
2. Cutaneous abnormality such as an infection at the proposed sampling site

Note. There are no data to confirm that uncorrected bleeding diathesis (prothrombin time or partial thromboplastin time greater than 2 times normal, International Normalized Ratio [INR] >1.5, platelets <50,000, or a creatinine level >6) or concurrent use of anticoagulants increases the risk of hemorrhagic complications. However, one must consider the risks and benefits for each procedure before proceeding without cessation of anticoagulant therapy or correction of coagulopathy or thrombocytopenia.

History

1. Patients with risk factors or a history suggestive of coagulopathy should have coagulation factors measured.
2. Screen for allergies to local anesthetics.
3. The urgency of the procedure (ie, the benefits of rapid diagnosis and treatment of empyema/parapneumonic effusion or relief of tension pneumothorax) can help guide the need to forgo correction of coagulopathy or thrombocytopenia or holding of anticoagulant medications.

Site Selection

1. Physical examination findings consistent with pleural effusions include decreased breath sounds, dullness to percussion, loss of tactile fremitus, and asymmetric diaphragmatic excursion.
2. A lateral decubitus film, ultrasound, or computed tomography scan of the chest can exclude alternative diagnoses that mimic pleural fluid on standard posteroanterior (PA) and lateral chest radiographs.
3. Using ultrasound for site selection is recommended by the British Thoracic Society guidelines on pleural procedures and is now widely considered standard of care in America. Ultrasound-assisted thoracentesis can be performed safely in patients on mechanical ventilation and has been shown to decrease the risk of complications, including hemorrhage.
4. Radiographic and physical examination can be used for site selection if ultrasound is not available, but at least 1 cm of fluid should layer out on a lateral decubitus film in order to safely sample an effusion without ultrasound assistance. Ultrasound assistance is recommended if two unsuccessful, or “dry taps,” are performed.

Note. If septations, hyperechoic fluid, or evidence of a complex pleural effusion are noted on ultrasound examination, chest tube placement should be considered in lieu of thoracentesis to allow for effective drainage and use of intrapleural lytic therapy if indicated.

Procedure

1. Explain the procedure, risks, benefits, and alternatives. Answer questions and obtain consent.
2. There are multiple commercially available procedure kits that simplify the gathering of needed equipment (Table 84.1 lists necessary equipment for thoracentesis).

TABLE 84.1 Materials Necessary for Thoracentesis

Sterile gloves	60-mL syringe	Green-top blood tube[d]
Mask	25-G needle[b]	Sterile dressing
Antiseptic solution[a]	22-G × 1.5-in needle[c]	Lavender-top tube[e]
Sterile drape or towels	Scalpel with No. 11 blade	Sterile specimen cups[f]
1% Lidocaine without epinephrine	Pleural catheter	Fluid collection bag
10-mL syringe	Sterile gauze	

[a]Chlorhexidine or betadine.

[b]To anesthetize skin.

[c]To anesthetize tract and pleura.

[d]For chemical analysis.

[e]For cell count.

[f]For cultures and cytology.

3. Sit the patient up with arms draped forward over a bedside table or procedure stand to maximize the intercostal space and amount of fluid in the posterior gutter. If the patient is intubated (or unable to sit up), our preference is to position the patient so that the intended side for thoracentesis is up.

4. With ultrasound assistance, identify the diaphragm between the mid-scapular line and the posterior axillary line and go one rib space up. Mark a site where at least 1.5 cm of fluid is between the chest wall and the underlying lung (Figure 84.1).

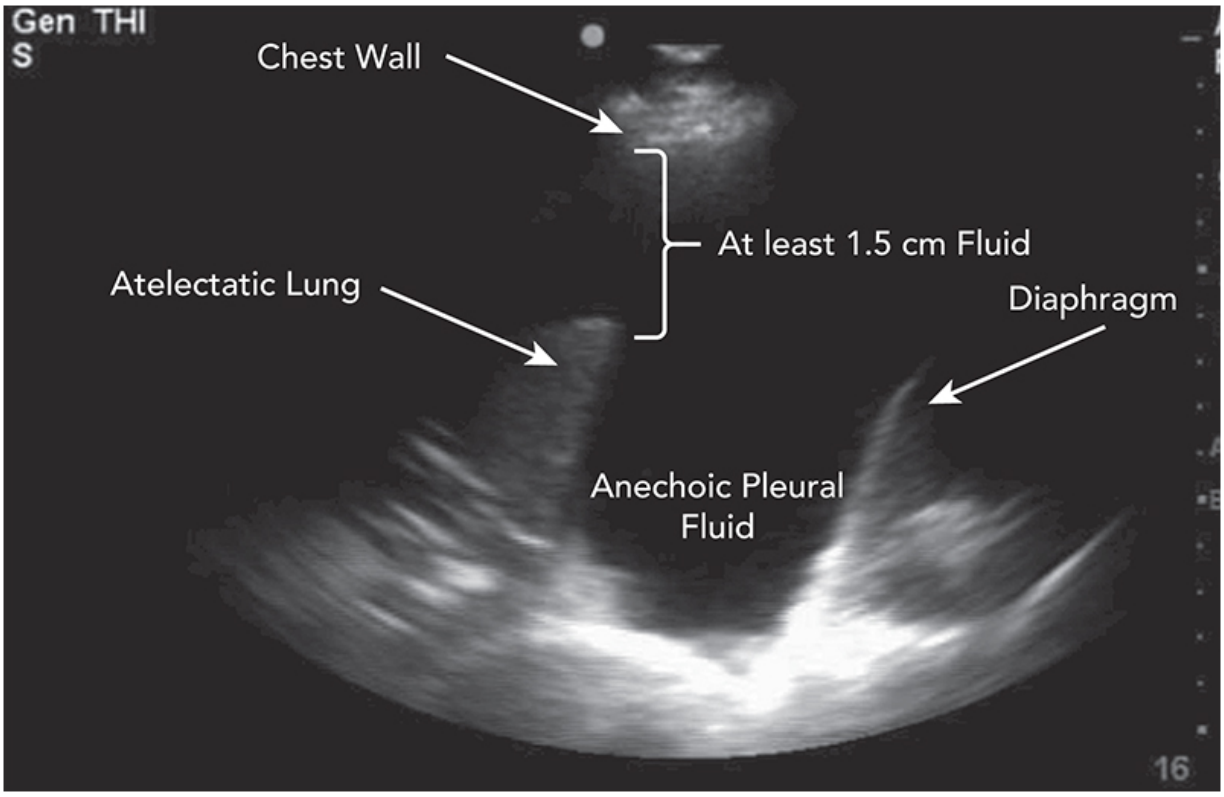

FIGURE 84.1 Ultrasound image depicting diaphragm and 1.5 cm of fluid between chest wall and underlying lung.

5. If ultrasound is not available, percuss down the chest until an area of dullness is reached and go one intercostal space below the area of dullness. Avoid the paraspinal area to avoid intercostal vessels. Do not go below the ninth rib interspace to avoid splenic or hepatic laceration (Figure 84.2).

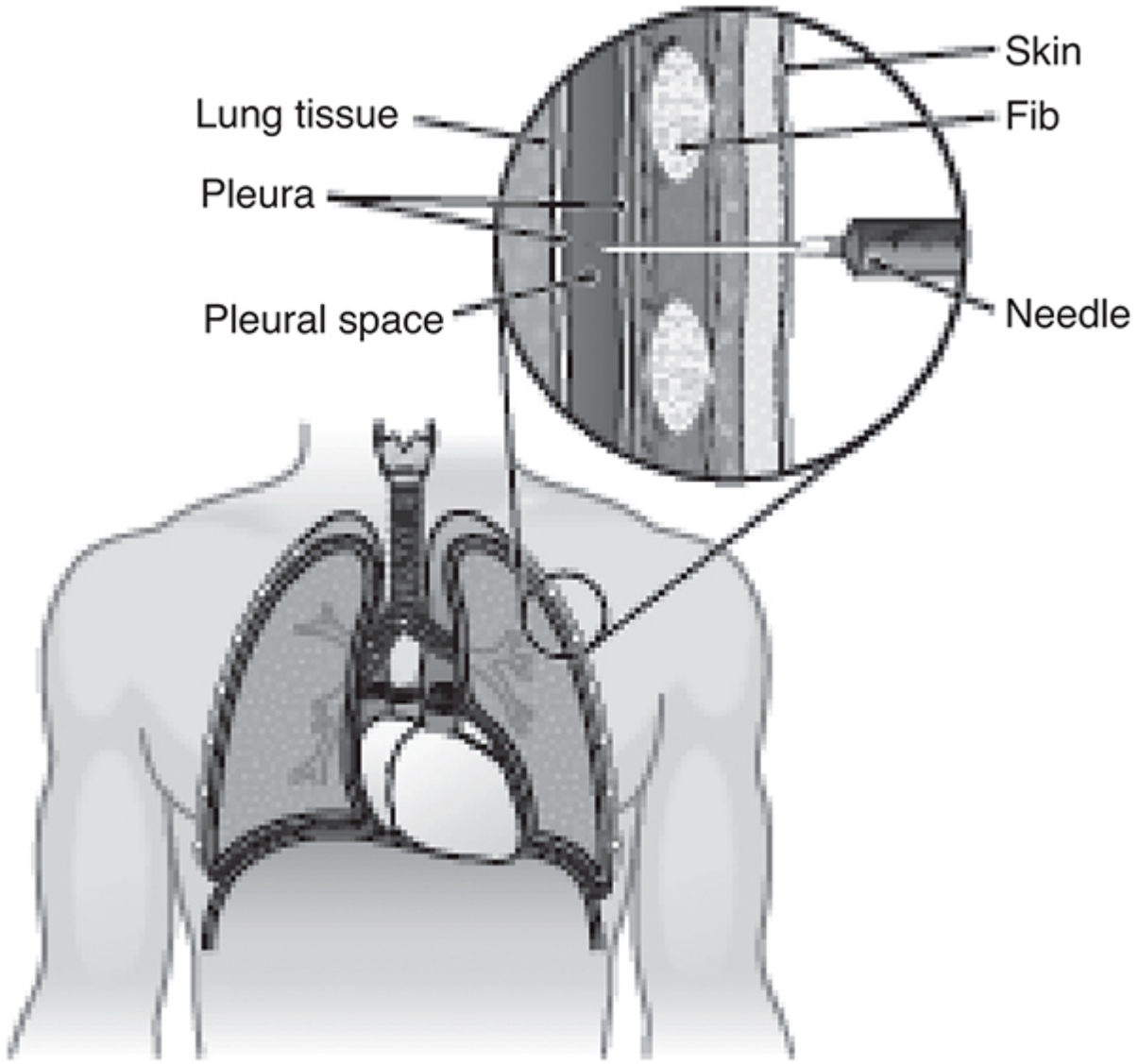

FIGURE 84.2 Schematic illustrating appropriate needle location for sampling and pleural effusion.

6. Don a mask and sterile gloves.
7. Cleanse the chosen site with an appropriate antiseptic (chlorhexidine or betadine).
8. Cover the surrounding area with sterile drape or towels.
9. Use a 25-gauge needle attached to a 10-mL syringe filled with lidocaine to create a skin wheal over the top of the appropriate rib.
10. Use a 22-gauge needle to advance through the wheal while aspirating. It is important to keep the needle perpendicular to the skin surface at all times. If ultrasound assistance was used for site

selection, maintain the needle in the same orientation that the ultrasound probe was held during site selection. Advance the needle a few millimeters at a time, aspirating and injecting lidocaine with each stop, until fluid is aspirated. At this point, withdraw slowly until flow of fluid stops, and inject the remainder of lidocaine to properly anesthetize the pleura. Remember, the skin, top of the rib, and parietal pleura require the most anesthetic. A minimum of 10 to 15 mL of lidocaine is recommended to provide adequate local anesthesia.

11. If using a needle without a catheter device, insert needle into previously anesthetized tract until fluid is aspirated. Collect fluid for studies.

12. If using a needle with a catheter device, first make a skin nick with a scalpel. Insert the needle and catheter device through the skin nick and advance while aspirating, making certain to keep the device in the same orientation that was used during lidocaine injection. After fluid is aspirated, advance the needle and catheter 2 to 3 mm further into the pleural space. Then advance the catheter over the needle and into the pleural space while preventing the needle from advancing further. Remove the needle, leaving the catheter in place.

13. Using a large syringe, remove fluid for studies. Of note, although submission of large amounts of cytology fluid is commonly advocated, the yield for diagnosis appears to be independent of the fluid amount submitted. (See Chapter 17, Pleural Disorders in the Intensive Care Unit, for further guidance on fluid analysis.)

14. If performing a therapeutic procedure, connect the catheter to a syringe and collection bag system. Vacuum bottles or wall suction devices **should not** be used for thoracentesis, as this has been associated with an increased risk for pneumothorax, pain, early procedure termination, and may increase risk for re-expansion pulmonary edema (REPE).

15. Cough is expected as the underlying atelectatic lung re-expands. Shoulder/scapular pain or unilateral posterior chest pain is thought to likely be due to catheter-induced irritation of the diaphragm or pleura. Slowing the rate of fluid removal or temporarily stopping the procedure until the pain improves is acceptable.

16. It is generally recommended that the procedure be stopped when the patient develops symptoms of intractable cough or anterior chest/neck discomfort (as these are thought to be signs of increasingly negative pleural pressures) or after approximately 1,500 mL of pleural fluid is removed to avoid REPE. Alternatively, one can monitor pleural manometry, if available, and keep pleural pressures greater than −20 cm H_2O, although this is not routinely recommended.
17. Remove the catheter during exhalation, as this is when intrathoracic pressure is positive, decreasing the likelihood of entertainment of air, that is, pneumothorax. Cover site with a sterile dressing.
18. Chest x-rays are commonly performed to exclude pneumothorax, but data suggest that they may not be needed unless there are concerning symptoms or problems with the procedure that suggests that the lung may have been punctured.

Complications

Complications can be separated into major complications, such as pneumothorax, significant bleeding, or REPE, and minor complications, such as pain or failed procedure/dry tap.

Operator experience and ultrasound assistance play a significant role in the risk of complications, emphasizing the importance of having the proper background knowledge and experience in the performance of the procedure. For example, use of ultrasound has been associated with a 39% reduction in bleeding complications.

REPE is a feared, but rare complication of therapeutic thoracentesis, with an estimated incidence of clinically significant REPE of less than 1%. The pathophysiology is unclear but has been hypothesized to be due to excessive negative pleural pressure during pleural drainage procedures. Symptoms include anterior chest or neck pain/pressure and intractable cough. Therapy is supportive.

Factors that affect hemorrhagic complications include the number of needle passes and the location on the chest, with decreasing risk observed further from the spine the site is. Although guidelines recommend correcting thrombocytopenia (platelets <50,000) or coagulopathy (INR >1.5), there is limited data supporting this practice, and growing literature suggests it is unnecessary. We recommend considering the risk-to-benefit ratio for each case individually when considering correcting bleeding risk.

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Fong C, Tan CWC, Tan DKY, See KC. Safety of thoracentesis and tube thoracostomy in patients with uncorrected coagulopathy: a systematic review and meta-analysis. *Chest.* 2021;160(5):1875-1889.

Systematic review and meta-analysis including 18 studies evaluating the major bleeding and mortality rate among patients with uncorrected disease or drug-related coagulopathy.

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Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? *Chest*. 2003;123(2):418-423.

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85 Pulmonary Artery Catheterization

Jon Greenberg

Since its inception in the 1970s, the clinical use of the pulmonary artery catheter (PAC) has been controversial. The PAC was originally developed by Swan and Ganz as a means to obtain direct pressure measurements from the right atrium (RA), right ventricle (RV), pulmonary arteries (PAs), and pulmonary capillary wedge pressure (PCWP) as well as a means of measuring cardiac output (CO). The use of PACs gained rapid acceptance when it became evident that physician assessments of hemodynamic parameters were often inaccurate. Subsequently, PACs became widely utilized in a wide variety of intensive care unit (ICU) patients, with bedside management frequently relying on measurements from the PAC. However, the clinical benefit of this approach had not been adequately validated through research or clinical trials.

Numerous subsequent trials conducted in diverse patient populations (including surgical patients, patients with acute myocardial infarction, congestive heart failure, and acute lung injury) have failed to demonstrate any benefits and, in some cases, have even shown increased potential for patient harm associated with the use of PACs. A study by the acute respiratory distress syndrome clinical trials network found no difference in outcomes of patients with this syndrome who had their fluid balance guided by use of central venous pressure monitoring through a standard central venous catheter (CVC) or placement of a PAC. The pendulum has swung, and routine use of the PAC has largely decreased, even to the point of avoidance. PACs still have a role in patients with PA hypertension, congenital heart disease, and in patients with complex fluid management issues. In addition, there have been recent meta-analyses showing mortality benefit in complete hemodynamic profiling with PACs in patients with cardiogenic shock. Moreover, patients in cardiogenic shock benefited from shorter time to mechanical circulatory support (MCS) with earlier PAC placement.

Noninvasive techniques to assess hemodynamic parameters have been attempted and studied, which has helped to reduce dependence on

the PAC. As medical technology improves and increasing numbers of clinicians gain expertise with bedside cardiac ultrasound, it is possible that the number of patients who would benefit from PAC placement will decrease. The clinician using the PAC needs to ask how the information obtained from a PAC will change the management of a specific patient, and be alert to possibly the greatest danger of the device: misinterpretation of its hemodynamic measurements. The PAC should be left in place for the shortest time possible as the end tends to drift as it becomes more malleable within the body. PACs should be placed in patients who have been carefully selected with the understanding that it is unlikely to alter the clinical course of patients who fall outside certain physiologic states (Table 85.1).

TABLE 85.1 Contraindications to, Indications for, and Complications of Pulmonary Artery Catheter Placement

Relative Contraindications	Complications
Left bundle branch block	Complications related to introducer placement
Severe coagulopathy	• Pneumothorax • Hemothorax • Hematoma at the site of insertion • Infection at the insertion site
Indications	

Relative Contraindications	Complications
Diagnosis and management of shock states Oliguric acute renal failure Assessment of volume status Titration of therapy for cardiogenic shock Decision to initiate MCS in cardiogenic shock Management of MCS in cardiogenic shock Diagnosis of PAH Vasodilator testing in PAH Diagnosis of multiple cardiac disorders, including pericardial constriction, VSD, RV infarction	Complications related to PAC use • Arrhythmias • Right bundle branch block • Complete heart block (preexisting left heart block) • Catheter thrombosis • Pulmonary embolism • Pulmonary infarct
Perioperative management of major procedures	• Line sepsis • Pulmonary artery rupture • Pulmonary artery pseudoaneurysm • Valvular damage • Cardiac perforation • Catheter kinking

MCS, mechanical circulatory support; PAC, pulmonary artery catheter; PAH, pulmonary arterial hypertension; RV, right ventricle; VSD, ventricular septal defect.

Procedure Technique

The easiest insertion sites are normally the right internal jugular (RIJ) vein or the left subclavian vein; however, femoral or even brachial vein sites can be used. This procedure can be performed in various locations in the hospital, but the most common are in the cardiac catheterization lab (which often uses fluoroscopy to guide placement) and at bedside in the ICU. Prior to starting the procedure, an evaluation of any contraindications to the procedure should be made, and consent should be obtained. In cases with suspected right-sided heart pathologies and/or PA hypertension, consideration should be given to placing the PAC with fluoroscopic guidance, if possible, as direct visualization enhances the ability to pass the PAC in these difficult cases.

The intravenous lines, pressure bags, transducers, and zeroing apparatus should all be assembled and ready prior to the sterile insertion of the PAC. It is beneficial to have an assistant or nurse who is trained in bedside management of PACs available for the procedure. A sterile procedural field should be used, with strict attention to handwashing, mask and cap usage, sterile glove and gown use, as well as full-length drapes and a sterile ultrasound probe cover. It is standard of care to utilize ultrasound guidance, if possible, when accessing the vein. The introducer catheter is inserted in a similar manner to a CVC using the Seldinger technique. The introducer catheter is slightly different in that the dilator is typically advanced through the introducer rather than as a separate piece of equipment, as occurs with a regular CVC insertion. There are cases where performing the first dilation with the dilator outside the introducer and then placing the dilator back through the introducer can prevent kinking of the introducer in patients with excess subcutaneous tissue. The guidewire and dilator are removed together at the conclusion of the introducer insertion, which leaves the introducer alone in the vessel.

The PAC (see Figure 85.1) should have all ports flushed and the balloon checked for leaks prior to insertion. In addition, the operator should check that the balloon tip does not protrude beyond the inflated balloon as this can increase the risk of vascular rupture. All ports of the PAC should be attached to the pressure transducers and flushed prior to insertion. Waving of the catheter tip prior to insertion with verification of a waveform on the monitor confirms that the catheter ports are correctly attached. Prior to starting the procedure, a final check to verify that the protective catheter sheath has been inserted over the catheter should be performed. The sheath can be attached to the introducer with the entirety of catheter manipulation taking place from outside the sheath, or the sheath can be slid to the back of the catheter and secured once the catheter is in adequate position. The catheter should be oriented prior to insertion to match the natural curve in the catheter to the projected course through the vasculature. Occasionally, placing the catheter in a sterile ice bath can assist with successful placement.

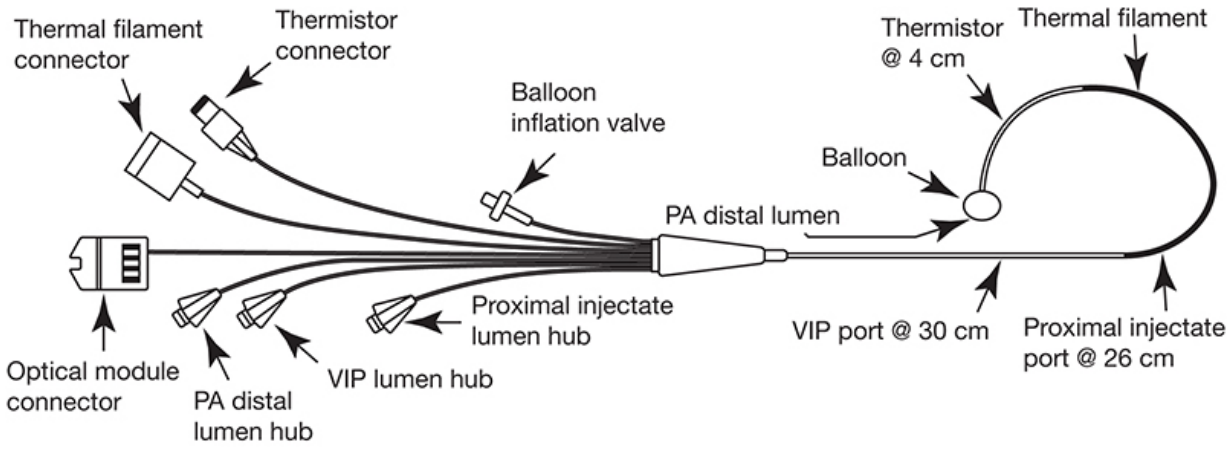
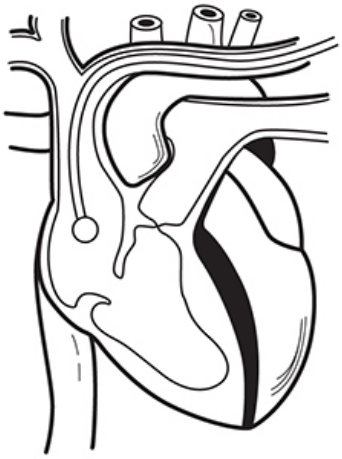
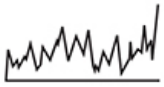
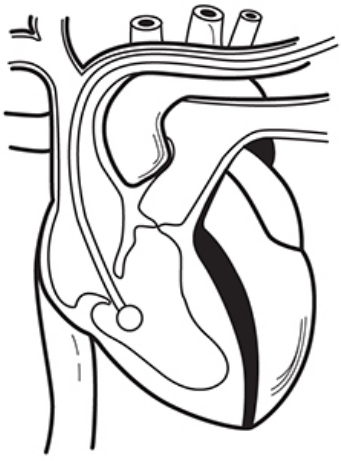
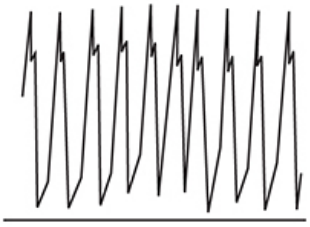
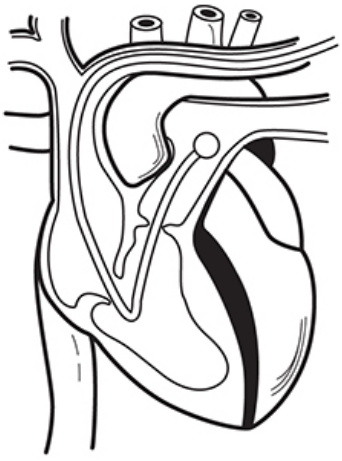
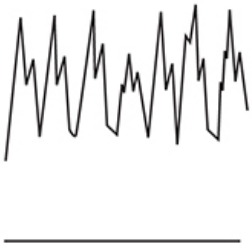
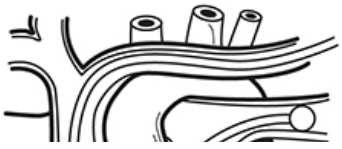


FIGURE 85.1 **Pulmonary artery (PA) catheter.** (Used with permission of John Wiley & Sons, from Clark SL, Phelan JP. *Critical Care Obstetrics*. 2nd ed. Blackwell Scientific; 1990:63; permission conveyed through Copyright Clearance Center, Inc)

The PAC is advanced through the introducer, and when the catheter tip is in the RA, the balloon should be inflated gently. The distance from the insertion site to the RA will vary depending on site, but is usually 15 to 20 cm from the RIJ or left subclavian sites. Once the balloon is inflated and the lock on the inflating syringe has been activated, the catheter is advanced steadily and the waveforms on the monitor are inspected. It is often helpful for the proceduralist to call out the depth of the catheter in 5 cm increments as it is being advanced. As the catheter is advanced from the RA to the RV, the waveform will change from a CVP waveform to an RV waveform, which will be noted by an increase in the systolic amplitude of the observed waveform. This normally occurs at approximately 30 cm (from an RIJ approach). The passage of the catheter through the RV is arrhythmogenic and should not be of prolonged duration. As the catheter tip traverses the pulmonary valve, conversion of the RV waveform to a PA waveform is identified by an increase in the diastolic pressure and the development of a dicrotic notch in the tracing (often at ~40 cm). This is commonly referred to as the "diastolic step-up." Difficulty in traversing the pulmonary valve is common in patients with PA hypertension from any cause. If excessive catheter length has been advanced without this transition occurring, the most likely explanation is that the catheter is coiled in the RV. If this occurs, the balloon should be deflated and the catheter should be withdrawn

until an RA tracing is obtained (at ~20 cm). The balloon should then be reinflated, and the procedure attempted again. In patients where placement is difficult, there is often some benefit in repositioning the patient under the sterile drape with their left side down and/or the head of bed slightly elevated. The PCWP tracing is identified by loss of the arterial tracing to a flatter tracing of lower amplitude than the PA diastolic pressure (often at ~50 cm). (See Figure 85.2 for the pressure tracings obtained as the catheter advances.) If multiple attempts at the bedside are unsuccessful, it may be necessary to have the PAC placed under fluoroscopic guidance in the catheterization lab.

	Catheter position	Waveform	Normal pressure range (mm Hg)
Right atrium			Mean 5-12
Right ventricle			Systolic 15-25 Diastolic 0-8
Pulmonary artery			Systolic 15-25 Diastolic 8-15 Mean 10-17
ry			

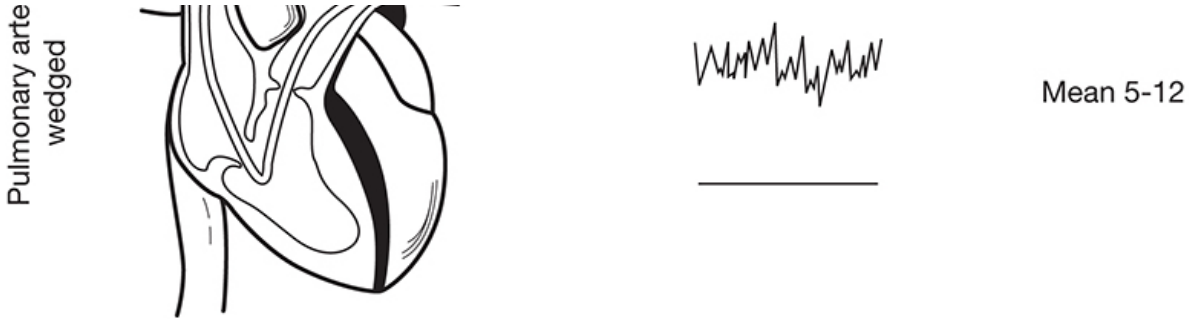


FIGURE 85.2 **Pulmonary artery catheter placement.** Catheter position, corresponding waveforms, and pressures are shown. (Used with permission of John Wiley & Sons, from Clark SL, Phelan JP. *Critical Care Obstetrics*. 2nd ed. Blackwell Scientific; 1990:63; permission conveyed through Copyright Clearance Center, Inc)

Once the PCWP is identified, the balloon should be deflated and the PA waveform observed. Gentle reinflation of the balloon while feeling for increased resistance and monitoring the waveform for overwedging is crucial. The 1.5-mL balloon should be fully inflated when a wedge tracing is obtained. If a wedge tracing is obtained and the balloon is only partially inflated, this signifies that the catheter tip is too distal and increases the risk of PA rupture with full inflation of the balloon. In this scenario, the catheter should be gently withdrawn 1 to 2 cm with the balloon deflated, and the balloon inflation procedure performed again to obtain a wedge tracing optimally at full balloon inflation. If there is no wedge tracing obtained with full inflation of the balloon, the catheter should be advanced with the balloon inflated until a wedge tracing is obtained. The catheter should never be withdrawn with the balloon inflated and should never be advanced without the balloon inflated, as this can result in perforation of the heart or a PA.

Once insertion is completed, the distance of insertion from the introducer site should be noted and recorded as a reference point. The catheter should be secured with tape and a sterile dressing, and the introducer should be sutured in place. A chest x-ray (CXR) should then be obtained to verify catheter course, tip position, and to rule out any complications from the procedure, such as a pneumothorax. Point-of-care ultrasound (POCUS) can also be utilized to assess catheter position and to rule out pneumothorax but does not preclude the need to obtain a CXR. As the catheter warms up in the patient's body, it tends to soften and migrate distally, which increases the risk of overwedging, pulmonary

infarction, and PA rupture with balloon inflation. PAC position should be reevaluated with a daily CXR as well as bedside by cautious inflation of the balloon and inspection of the waveforms (Table 85.2). The PAC should be left in place for the shortest amount of time necessary.

TABLE 85.2 Examples of Hemodynamic Parameters Obtained by a Pulmonary Artery Catheter in Different Clinical Situations

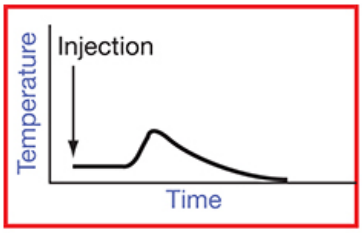
CVP (mm Hg)	RV Pressures (mm Hg)	PA Pressures (mm Hg)	PAOP (mm Hg)	CO (L/min)	SVR (dynes/s/cm^{-5})	Diagnosis
4	17-30/0-6	15-30/5-13	2-12	3-7	900-1,200	Normal
10	48/12	48/30	28	2.2	3,200	Cardiogenic shock
4	26/4	26/8	6	7	700	Sepsis
14	26/14	26/14	14	3.0	3,000	Cardiac tamponade
16	80/30	80/40	8	3.5	1,400	Pulmonary arterial hypertension
14	45/12	45/18	6	3	2,800	Pulmonary embolism (acute)
2	30/2	30/12	3	2.5	2,500	Hypovolemic shock

CO, cardiac output; CVP, central venous pressure; PA, pulmonary artery; PAOP, pulmonary arterial occlusion pressure; RV, right ventricle; SVR, systemic vascular resistance.

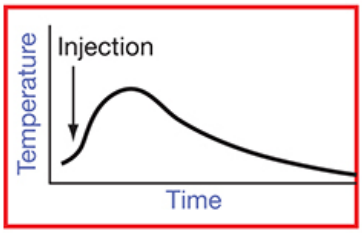
Cardiac Output Determination

After verifying the correct placement of the PAC, hemodynamic data can be obtained. The catheter system must be exposed to atmospheric air to establish the zero point for pressure measurement, and the catheter transducer must be referenced to the level of the heart. CO can be determined using both thermodilution and Fick calculation methods. For thermodilution, a known volume (typically 5-10 mL) of cold saline is injected through the proximal port of the PAC, while the distal port, equipped with a thermistor, records the change in blood temperature over time, displaying it as the thermodilution curve. The area under the thermodilution curve is proportional to the CO (PA flow rate), assuming there are no intracardiac shunts (which can falsely elevate CO) or tricuspid regurgitation (which can falsely lower CO). Normally, three thermodilution curves with minimal variance (<10%) are utilized to determine the mean CO, employing the Stewart-Hamilton equation. Notably, there have been advancements in catheter technology with PACs that now perform thermodilution CO calculations periodically in an automated fashion. Figure 85.3 shows various thermodilution curves.

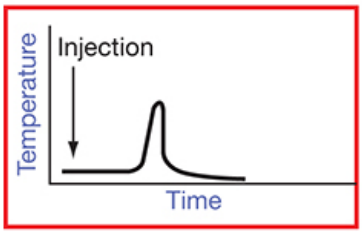
The Fick equation can also be used to calculate the CO. The Fick principle is stated as follows:



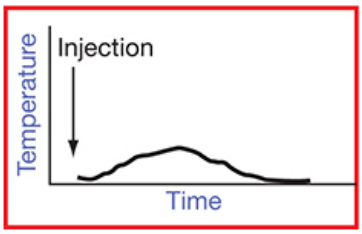
Normal thermodilution curve
With an accurate monitoring system and a patient who has adequate CO, the thermodilution curve begins with a smooth, rapid upstroke and is followed by a smooth, gradual downslope. The curve shown at the left indicates that the injectant instillation time was within the recommended 4 seconds and that the temperature curve returned to baseline.



Low CO curve
A thermodilution curve representing low CO shows a rapid, smooth upstroke (from proper injection technique). However, because the heart is ejecting blood less efficiently from the ventricles, the injectant warms slowly and takes longer to be ejected from the ventricle. Consequently, the curve takes longer to return to baseline. This slow return produces a larger area under the curve, corresponding to low CO.



High CO curve
Again, the curve has a rapid, smooth upstroke from proper injection technique. However, because the ventricles are ejecting blood too forcefully, the injectant moves through the heart quickly and the curve returns to baseline more rapidly. The smaller area under the curve suggests higher CO.



Curve reflecting poor technique
This curve results from an uneven and too slow (taking >4 seconds) administration of injectant. The uneven and slower than normal upstroke and the larger area under the curve erroneously indicate low CO. A kinked catheter, unsteady hands during the injection, or improper placement of the injectant lumen in the introducer sheath may also cause this type of curve.

FIGURE 85.3 **Cardiac output (CO) measurement.** Analyzing thermodilution curves.

Oxygen consumption (Vo_2) is normally estimated. Vo_2 consumption at rest is typically estimated to be 125 mL/min/m^2, and for patients aged 70 years or above, it is estimated to be 110 mL/min/m^2. Alternatively, Vo_2 can be estimated using a nomogram based on the patient's age, height, and weight. The arteriovenous oxygen content calculation requires a simultaneous arterial blood gas (Sao_2) and sampling of blood from the distal port of the PAC (Svo_2) and is calculated as follows:

$$\text{Arteriovenous oxygen content difference} = 1.34 \times \text{Hemoglobin concentration} \times (Sao_2 - Svo_2)$$

Pressure measurements should all be measured at end exhalation, when intrathoracic pressure most approaches atmospheric pressure. The use of a mainstream end-tidal CO_2 detector is useful to determine this point in intubated patients. In nonintubated patients, review of the hemodynamic tracings can identify fluctuations in pressure associated with normal respiration and end exhalation can be identified. If the patient is on supplemental oxygen, a nasal cannula, which measures end-tidal CO_2, can also be helpful. Utilization of all the hemodynamic data obtained from the catheter, together with knowledge of the patient's clinical scenario, can greatly aid in the interpretation of the data.

The PAC has a unique ability to identify diverse etiologies of shock, including hypovolemic, cardiogenic, and distributive/septic shock. Patients presenting with undifferentiated shock can benefit from PAC placement to identify the main mechanism driving their shock. In addition, patients with predominantly RV dysfunction and patients with pericardial tamponade can be identified. The use of continuous oximetry during catheter insertion can also identify step-ups in oxygen saturations, which can help diagnose intracardiac left-to-right shunts.

Titration of inotropes, fluids, and vasodilators can be performed with serial measurements from the PAC to optimize tissue oxygen delivery and hemodynamics. Patients with cardiogenic shock who would be candidates for MCS have recently been shown to have mortality benefits from early PAC placement. The PAC pendulum has swung back and forth since their introduction, and as with any critical care intervention, proper patient selection is paramount to extracting clinical benefit.

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Bootsma IT, Boerma EC, de Lange F, Scheeren TWL. The contemporary pulmonary artery catheter. Part 1: placement and waveform analysis. *J Clin Monit Comput*. 2022;36(1):5-15.

86 Alternative Hemodynamic Monitoring

Cameron Upchurch

A fundamental goal in managing the patient who is critically ill is to ensure that the delivery of oxygen (Do_2) is adequate for the patient's oxygen consumption ($\dot{V}o_2$) needs, as described in the following equation:

$$Do_2 = co \times Cao_2,$$

where co is the cardiac output (L/min) and Cao_2 is the oxygen content of arterial blood, including the oxygen bound to hemoglobin and the oxygen dissolved in arterial blood, or:

$$Do_2 = co \times [(1.34 \times Hb \times Sao_2) + (0.0031 \times Pao_2)] \times 10,$$

where 1.34 is the hemoglobin (Hb) coefficient (1.34 mL O_2 binds to 1 g Hb), Sao_2 is the oxygen saturation of arterial Hb, 0.0031 is the solubility O_2 coefficient (0.0031 mL of O_2 gas is dissolved in 100 mL of blood), and Pao_2 is the partial pressure of oxygen in arterial blood. Cao_2 is multiplied by 10, assuming [Hb] is in g/dL. From a simple arterial blood gas, Cao_2 can be calculated. However, the clinician is left with the challenge of measuring CO. There are several hemodynamic monitoring techniques aimed at quantifying CO to aid in patient management.

No hemodynamic monitoring technique can improve patient outcomes simply by being utilized. The ideal hemodynamic monitor should provide accurate and reproducible dynamic measurements of clinically relevant variables that are able to guide therapy. It should

be easy to use with rapid response times, be operator-independent, and cause no harm. The perfect system does not exist, and different approaches may be required in a single patient during different phases of their illness. There are several minimally invasive or noninvasive techniques that estimate CO. The most commonly used and validated techniques to estimate CO include the following:

- Aortic Doppler: Either minimally invasively with an esophageal Doppler probe or noninvasively via a transcutaneous approach, or via point-of-care cardiac ultrasound
- Transpulmonary thermodilution (TPTD): Minimally invasive with a central venous catheter and arterial catheter
- Pulse contour analysis: Minimally invasive with a peripheral arterial catheter or noninvasively with applanation tonometry or volume clamp methods
- Partial carbon dioxide (CO_2) rebreathing: Noninvasively with a breathing loop
- Thoracic electrical bioimpedance and bioreactance: Noninvasively with surface electrodes/sensors

Several other invasive techniques to quantify CO—such as pulmonary artery (PA) catheter placement and thermodilution and/or the Fick method—and noninvasive techniques—such as cardiac ultrasound, either transthoracic or transesophageal—are detailed in other chapters (Chapters 85, Pulmonary Artery Catheterization and Chapter 90, Basic Critical Care Ultrasound, respectively). Furthermore, there are other techniques aimed at informing the clinician regarding the perfusion status or the Do_2:$\dot{V}o_2$ balance of the patient, such as capillary refill time, sublingual tissue capnometry, near-infrared spectroscopy tissue oximetry, and venous to arterial partial pressure of carbon dioxide (v-a Pco_2), which are outside the scope of this chapter.

Aortic Doppler

Aortic Doppler can be used to measure aortic blood flow velocity and calculate CO. Aortic Doppler can be used, most commonly, via an esophageal probe, and less commonly, owing to its decreased accuracy, transcutaneously. Aortic Doppler, via esophageal Doppler, has been utilized in various situations, including trauma patients, medical intensive care units (ICUs), intraoperative assessment, and postoperative care.

Measurement of CO with the esophageal Doppler is based on measuring the velocity of blood flow through the descending thoracic aorta. The technique involves placing a transducer into the esophagus and rotating the probe to obtain an optimal ultrasound signal parallel to aortic blood flow. Blood flow velocity is measured by tracking changes in the frequency of reflected sound waves. Stroke volume (SV) is estimated from the derivation of a velocity-time integral (VTI) multiplied by the aortic cross-sectional area (Figure 86.1). Once SV is calculated, CO is determined (CO = heart rate × SV). This same method of calculating CO can be utilized noninvasively with point-of-care cardiac ultrasound by measuring the VTI through the left-ventricular outflow tract (LVOT) with pulsed-wave Doppler, coupled with measuring the diameter of the LVOT to calculate the cross-sectional area of the LVOT (see Chapter 90, Basic Critical Care Ultrasound, for more specific details).

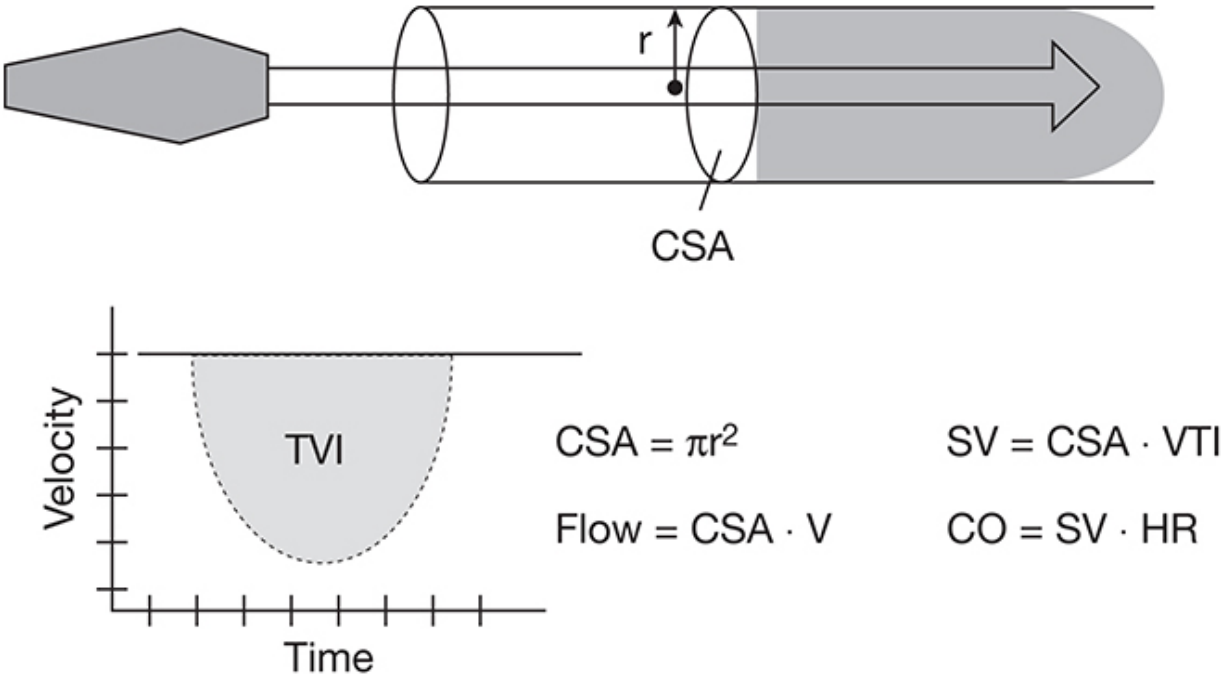

FIGURE 86.1 **Schematic representation of the method for determining volumetric flow**. This method is applicable for any laminar flow for which the cross-sectional area (CSA) of the flow chamber can be determined. The product of CSA and the velocity-time integral (VTI) is stroke volume (SV). Cardiac output (CO) can be calculated as the product of SV and heart rate (HR). See text for further details.

In addition to SV and CO, the esophageal Doppler provides a measure of preload termed corrected flow time (FTc). FTc is systolic flow time corrected for heart rate and is represented on the monitor display as the waveform's base. Normal values range between 330 and 360 ms; vasoconstricted states show decreased FTc and vasodilated states show increased FTc. The maximum or peak velocity is the waveform's height and can serve as a measure of left ventricular contractility. The normal range for peak velocity declines with age.

Thus, FTc can provide insights into vasoconstricted versus vasodilated states, while peak velocity can suggest high- versus low-output states. Following both FTc and peak velocity help to optimize resuscitation efforts in a wide spectrum of patients and clinical situations. For example, in a vasoconstricted state, such as in

hypovolemic shock, the monitor displays a narrow waveform base with a corresponding decrease in FTc (<330 ms) and a relatively normal peak velocity. Administration of fluid would widen the waveform base or lengthen the FTc. In cases where the underlying condition is myocardial depression, the initial waveform shows a low peak velocity and normal to low FTc. Inotropic therapy can improve the peak velocity or contractility in such a situation (Figure 86.2).

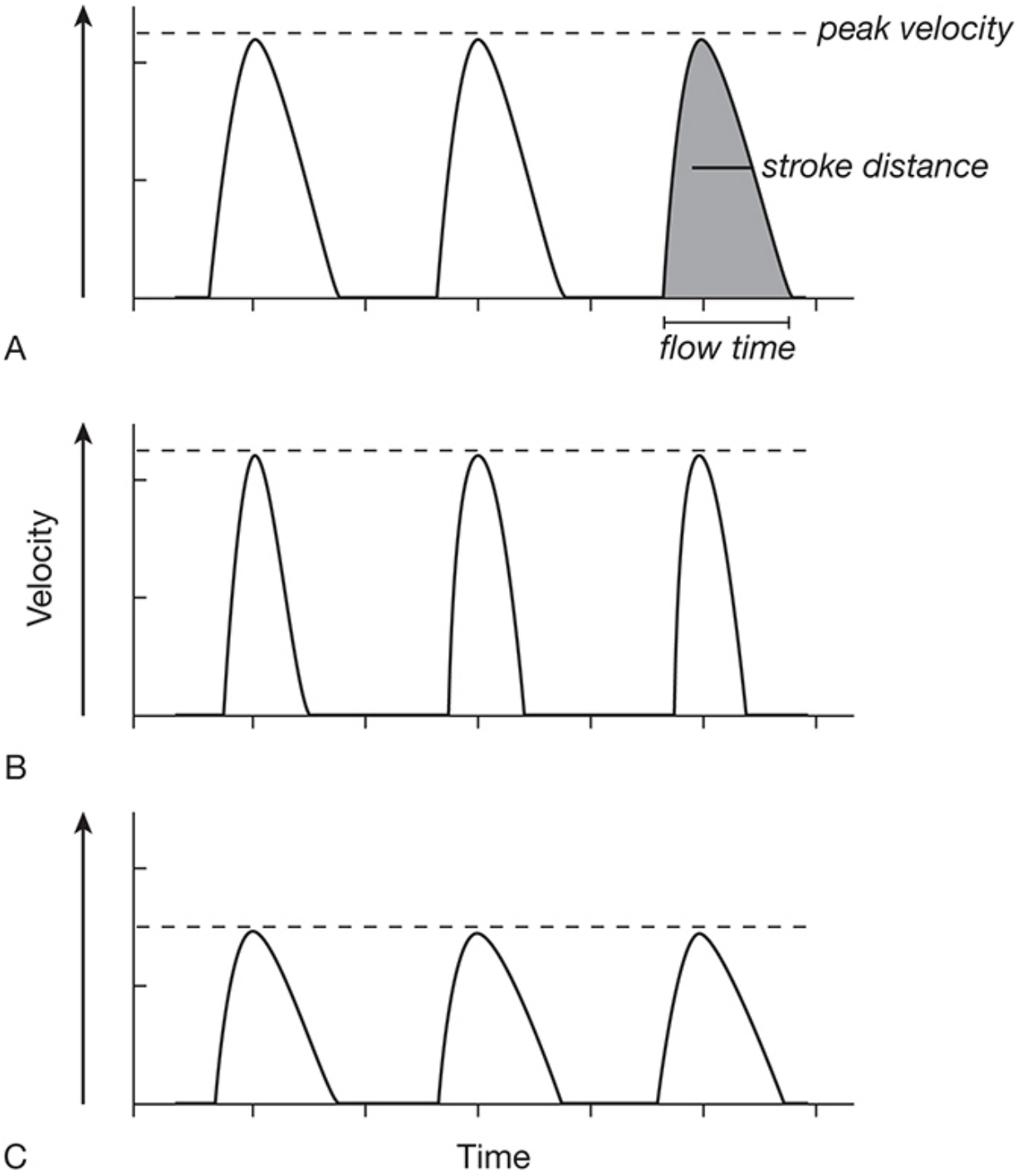

FIGURE 86.2 Schematic diagram of esophageal Doppler waveforms obtained during (**A**) normovolemia, (**B**) hypovolemia, and (**C**) left ventricular failure. The primary measurements obtained during esophageal Doppler monitoring are stroke distance (the area under the waveform during systole), the peak velocity, and the ejection time during systole ("*flow time*"). Note that during hypovolemia and heart failure, stroke distance is decreased. In

addition, ideally during hypovolemia, flow time is decreased but peak velocity is maintained, whereas during heart failure, flow time is normal but peak velocity is reduced. (From Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol.* 2006;291(6):L1118-L1131, used with permission.)

The major advantage of the esophageal Doppler is its ability to rapidly obtain a set of hemodynamic numbers that are generally easy to interpret. The probe is placed orally and advanced until reaching the midthoracic area, approximately 35 to 40 cm. It is possible to leave the esophageal Doppler in place for up to 72 hours, but it is important to test the position of the probe to ensure an optimal signal. The device is considered safe for use in most patients, including patients with coagulopathies. However, probe placement in patients with known varices is a relative contraindication.

One drawback of this technique is its limitation to sedated and mechanically ventilated patients. There are also several assumptions in the calculation of SV and CO that affect its ability to give precise measurements. SV is estimated from the proportion of blood flow that reaches the descending aorta. It is assumed that there is a constant 70/30 division of flow between the descending aorta (70%) and the brachiocephalic arteries supplying the head, neck, and upper extremities (30%), which may not be true, especially in patients in shock. The cross-sectional area of the aorta is estimated using a nomogram that takes into account characteristics of the patient, such as age, sex, and weight. Therefore, if significant aortic pathology (aneurysm or dilation) is present, the absolute derived values may not be accurate. The mathematical model also assumes that the aorta is cylindrical with constant laminar flow running parallel to the esophagus. In reality, flow may be turbulent due to arrhythmia, anemia, or aortic valve disease. Body habitus, such as severe kyphoscoliosis, may limit the ability to obtain an appropriate signal.

The presence of any of these factors makes it difficult to obtain a consistent signal.

Esophageal Doppler monitoring is most useful when the device is used to obtain serial measurements to detect trends and responses to therapies. Absolute values are not as important as trend analysis, and this concept is explained in Chapter 87 (Functional Hemodynamic Monitoring). Improved outcomes utilizing esophageal Doppler–guided fluid administration and vasoactive titration management have been shown in intra- and postoperative patients and trauma patients, but there is a lack of outcome data in most ICU patients.

Transpulmonary Thermodilution

In contrast to the PA thermodilution technique (which requires placement of a PA catheter), TPTD measures CO by detecting a cold bolus within the peripheral arterial system. The cold injectate is administered through a central venous catheter and detected by a thermistor-tipped arterial catheter placed in the radial, axillary, or femoral artery. CO is then calculated by the Stewart-Hamilton equation, similar to PA catheter thermodilution (Chapter 85, Pulmonary Artery Catheterization). Commercial systems exist that combine TPTD with pulse contour analysis (which is calibrated against the TPTD CO measurement) to provide continuous CO reporting. A potential benefit of the TPTD technique is the ability to obtain CO readings, as well as other markers of preload (global end-diastolic volume [GEDV], intrathoracic blood volume [ITBV], and extravascular lung water [EVLW]), without the need for PA catheter placement. However, GEDV, ITBV, and EVLW are static markers of volume and do not indicate true fluid responsiveness, but rather indicate whether a patient may be fluid tolerant or intolerant.

TPTD measurements can be used not only to measure flow but also to measure the volume through which flow is measured (ie, from the point of injection to the point of detection). The derived volumes can be seen schematically in Figure 86.3.

- Intrathoracic thermal volume (ITTV) = CO × Mean transit time of the thermal indicator
- Pulmonary thermal volume (PTV) = CO × Downslope time of the thermal indicator
- Global end-diastolic volume (GEDV) = ITTV − PTV and provides a preload marker of moderate strength
- Intrathoracic blood volume (ITBV) = 1.25 × GEDV − 28.4 (mL)
- Extravascular lung water (EVLW) = ITTV − ITBV and may be used to help guide fluid administration or distinguish between hydrostatic pulmonary edema and acute lung injury

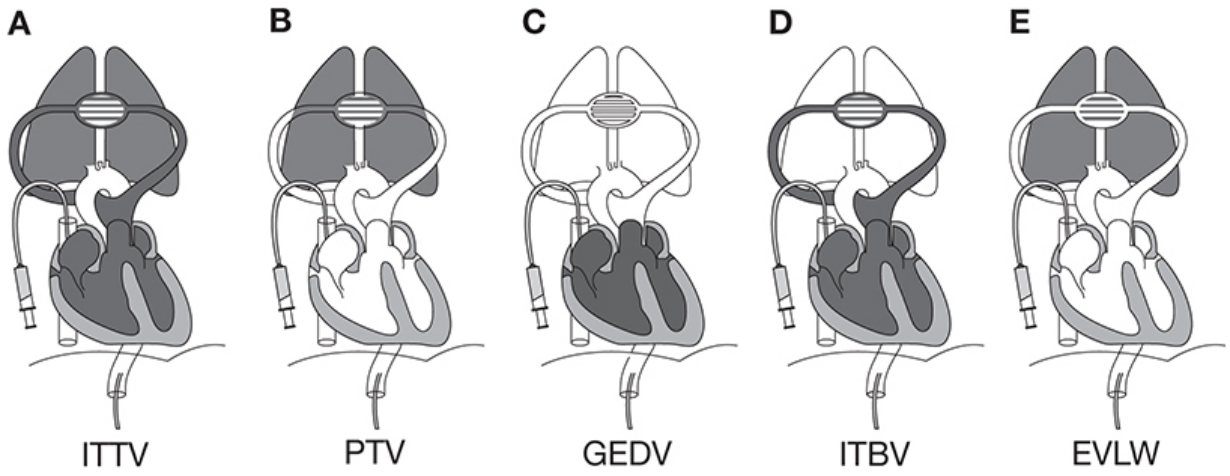

FIGURE 86.3 **Schematic diagrams of different volumes that can be measured (*dark shaded areas*) with the transpulmonary thermodilution technique**. EVLW, extravascular lung water; GEDV, global end-diastolic volume; ITBV, intrathoracic blood volume; ITTV, intrathoracic thermal volume; PTV, pulmonary thermal volume. (From Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol.* 2006;291(6):L1118-L1131, used with permission.)

The clinical use of EVLW is not clear. Increases in EVLW levels may serve as an indication of early pulmonary edema. It has been found that mortality tends to increase when EVLW rises above 15 mL/kg, both in general patients who are critically ill and specifically in

those with acute respiratory distress syndrome (ARDS). However, currently there is no established protocol for using EVLW in patients with sepsis or ARDS. The value for EVLW is subject to error in certain situations. It is found to be overestimated in cases of severe lung injury, right-to-left intracardiac shunt, and low CO states. It is underestimated in patients with acute pulmonary embolism or high positive end–expiratory pressure (PEEP), where the loss of perfusion affects the ability of the thermal indicator to detect all areas of lung water.

CO measurements obtained using TPTD have been shown to correlate well with PA catheter thermodilution method CO measurements, and its use measuring the EVLW has been shown to aid in the early identification of ARDS, prognostication, and successful prediction in extubation success.

Pulse Contour Analysis

Pulse contour analysis methods use the arterial pressure waveform to predict vascular flow and calculate SV by way of measuring the area under the curve of the systolic arterial pressure waveform. Most devices require calibration to provide a correction factor for differences in the arterial system. Indeed, there are several assumptions necessary to derive the aortic pressure waveform from the shape of the peripheral pulse. Therefore, some devices use either TPTD or lithium dilution techniques as a reference calibration point to derive CO. It should be noted that pulse contour analysis does not measure CO directly but estimates it using a proprietary algorithm.

The most validated pulse contour analysis devices require arterial line placement, and in systems requiring calibration with TPTD or lithium dilution, a central venous catheter is required as well. Systems that do not require TPTD or lithium dilution calibration use a correction factor based on age, sex, and body surface area to estimate CO instead.

There are several completely noninvasive devices that use pulse contour analysis technology to estimate CO. These include radial artery applanation tonometry and volume clamp methods. Radial artery applanation tonometry utilizes a transducer applied over an artery with an underlying bone, such as the radial artery, which allows pressure to be applied to compress the radial artery and transduce an arterial pulse wave. From this, systolic and diastolic pressures are obtained, which are used to derive an arterial pressure waveform from which pulse contour analysis is performed and algorithmically combined with age, sex, and weight to provide a continuous CO estimate. Volume clamp methods are also completely noninvasive, utilizing a cuff (often on a finger) that measures arterial pressure by constantly adjusting to maintain constant volume in the finger compartment. Infrared sensors detect changes in the artery diameter, allowing the generation of an arterial pressure waveform and pulse wave. CO is derived using pulse contour analysis in combination with demographic factors. However, potential limitations of these noninvasive pulse contour analysis methods may arise in patients with poor peripheral circulation, such as those with peripheral vascular disease or patients in shock, where measurements may not be reliably obtainable.

Each device uses a different mathematical model of pressure and flow that must account for the changes in aortic impedance, arterial compliance, and systemic resistance. Calibration is generally needed to derive the correction factors for these mathematical algorithms, and devices need to be recalibrated after significant hemodynamic changes.

Pulse contour analysis provides continuous CO monitoring, in contrast to TPTD or PA catheter thermodilution techniques, which are intermittent.

The CO provided by pulse contour analysis is subject to error as well. These devices are limited by dynamic changes in vascular resistance, which would require recalibration. This performance is also affected by the presence of aortic regurgitation, aortic aneurysm, arrhythmias such as atrial fibrillation, and dampened waveforms. These devices can provide useful information like pulse

pressure variation and SV variation as dynamic markers used as a surrogate for preload responsiveness in patients who are totally invasively mechanically ventilated (no spontaneous respiratory effort), in normal sinus rhythm, and on a ventilator with adequate tidal volumes (validation studies used 8 cc/kg or more). This concept is explained in Chapter 87, Functional Hemodynamic Monitoring.

Minimally invasive (utilizing an indwelling arterial line) pulse contour analysis has shown good agreement with PA catheter-derived thermodilution CO values in patients who are not critically ill. However, studies have shown limited accuracy and effectiveness in hemodynamically unstable patients. Completely noninvasive pulse contour analysis, such as radial artery applanation and volume clamp methods utilizing a finger cuff, is less well-validated in patients who are critically ill, with absolute values of CO measurements being less reliable. Nevertheless, these methods are more reliable in appropriately detecting changes in CO and its magnitude.

Partial Carbon Dioxide Rebreathing

This technique relies on the modified Fick principle to calculate CO. The Fick equation is based on the belief that oxygen uptake from the lung is completely transferred into the bloodstream. Therefore, CO is calculated as a ratio between oxygen consumption and the arteriovenous difference in oxygen content. In the partial CO_2 rebreathing technique, the Fick principle is applied to CO_2 instead of oxygen. The modified Fick equation is used to calculate CO from the change in the ratio of CO_2 production and end-tidal CO_2 (as a surrogate for arterial CO_2) before and after rebreathing. Intrapulmonary physiologic shunt and anatomic shunt can affect this equation by changing the blood flow participating in gas exchange. Some devices incorporate peripheral oxygen saturation and Pa_{O_2} from blood gases to account for shunting. Nonetheless, underlying lung disease, varying tidal volumes, and hemodynamic instability can alter the precision of this technique. Furthermore, CO measurements

have been shown to have a weak correlation with PA catheter thermodilution CO measurements in patients who are critically ill. Therefore, the partial CO_2 rebreathing technique is seldom used in clinical practice.

Thoracic Bioimpedance

In thoracic bioimpedance, SV is estimated from changes in electrical resistance over time as a low-magnitude, high-frequency current is applied through electrodes placed on the upper and lower body. The patient does not detect the low level of current, and this technique is completely noninvasive. The electrical current follows the path of least resistance, which aligns with aortic blood flow. When the left heart contracts, there is an increase in aortic blood volume, resulting in a decrease in impedance proportional to SV. To calculate SV, the amount of electrically participating tissue is estimated based on sex, height, and weight of the patient. The surrounding tissue fluid volume becomes important for the precision of impedance measurements.

This technique is sensitive to acute changes in tissue water content, such as pulmonary edema, effusions, and anasarca. The electrodes cannot be moved during the measurement, because it is a calculation of change over time. The calculation also depends on a constant R-R interval; therefore, arrhythmias can cause errors in the measurement of SV and, subsequently, CO. Measurements are also affected by temperature and humidity. Thoracic bioimpedance has been shown to have weak correlation to PA catheter thermodilution CO measurements in ICU patients. Therefore, its use in the ICU population is limited due to the aforementioned factors, and devices using bioreactance are considered more reliable.

Thoracic Bioreactance

Thoracic bioreactance devices measure bioreactance, specifically the phase shift in voltage across the thorax. These devices measure thoracic impedance, tracking changes in amplitude and direction (measured in degrees) of impedance. Pulsatile blood flow causes these phase shifts in impedance, and the vast majority of thoracic pulsatile flow is generated by aortic blood flow. Therefore, static thoracic fluid such as pulmonary edema, which may affect thoracic bioimpedance measurements, are less likely to induce a phase shift and thus less likely to affect bioreactance, which is only affected by pulsatile (or phasic) aortic flow. A sensitive phase shift detector is used to noninvasively measure these phase shifts from aortic flow and translates this change into SV that can be used to estimate CO. The system is totally noninvasive, comprising a high-frequency sine wave generator (75 kHz) and electrode stickers that establish electrical contact with the thorax. Two stickers are placed on each side of the thorax, and CO is determined separately from each side of the body, with the final noninvasive CO averaged from these two values. Bioreactance-based measurements are more accurate than bioimpedance techniques as they do not measure static impedance and do not depend on the distance between electrodes. Signals are averaged over 1 minute, allowing this technology to be used in patients with arrhythmias. However, bioreactance is not reliable in patients undergoing external pacemaking or during electrocautery. Validation studies have shown good correlation between bioreactance-derived CO and CO obtained by PA catheter thermodilution techniques, as well as with the esophageal Doppler, over a wide range of patient populations, including patients who are critically ill. There are conflicting data whether bioreactance can track changes in CO to functional challenges like fluid boluses and passive leg raises in different ICU populations.

Conclusion

Multiple minimally invasive and noninvasive devices exist to estimate CO. The decision to use one form of hemodynamic monitoring over

the other depends on understanding the limitations of each device and assessing each patient's unique situation. No single device has been shown to improve patient outcomes over another. Rather, the correct interpretation of the device's outputs in the context of its limitations, coupled with appropriate clinical assessment, is required to institute personalized therapeutic interventions for the specific patient at hand and improve their outcome.

SUGGESTED READINGS

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Gavelli F, Shi R, Teboul JL, et al. Extravascular lung water levels are associated with mortality: a systematic review and meta-analysis. *Crit Care.* 2022;26(1):202.

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Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol*. 2006;291(6):L1118-L1131.

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Marik PE. Noninvasive cardiac output monitors: a state-of-the-art review. *J Cardiothorac Vasc Anesth*. 2013;27(1):121-134.

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Morgan P, Al-Subaie N, Rhodes A. Minimally invasive cardiac output monitoring. *Curr Opin Crit Care*. 2008;14(3):322-326.

Reports the evidence to support using pulse contour techniques and a closer look at the different commercially available devices.

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87 Functional Hemodynamic Monitoring

Walter Schiffer and Adam May

Hemodynamic Assessment and Monitoring

Hemodynamic assessment and monitoring are fundamental to the diagnosis, characterization, and management of shock. Beyond correctly categorizing the type of shock present, it is important for clinicians to understand the complex interplay of hemodynamic influences on the cardiovascular system and how these factors impact the nature and degree of shock. This chapter reviews the essential tools and methods of hemodynamic assessment and monitoring, broadly characterizes the hemodynamic profiles of shock, and discusses the dynamic interactions between hemodynamic parameters in response to common clinical perturbations and treatments.

Noninvasive Hemodynamic Tools and Methods

PHYSICAL EXAMINATION

A thorough physical examination is essential for properly evaluating a patient's hemodynamic state. Basic physical examination findings, including, but not limited to, mental status, pulse palpation, capillary refill time, cardiac auscultation findings, jugular venous pulsation (JVP) assessment, skin color, and skin temperature can help clinicians determine the type and severity of shock present. For example, identification of altered mental status, diminished palpable pulses, delayed capillary refill, cool peripheral extremities, an S_3

heart sound, pulmonary rales, and an elevated JVP on physical examination indicates the presence of impaired cardiac output (CO), elevated intracardiac filling pressures, and increased systemic vascular resistance (SVR), a constellation of findings most consistent with cardiogenic shock. Alternatively, a patient in the early phases of septic shock may demonstrate altered mental status, warm extremities, bounding peripheral pulses, normal capillary refill, normal heart tones, clear lung sounds, and flat neck veins, suggesting increased CO, nonelevated intracardiac filling pressures, and decreased SVR.

NONINVASIVE BLOOD PRESSURE CUFF

Serial blood pressure (BP) measurements are fundamental to assessing a patient's hemodynamic state and response to medical interventions. Oscillometric BP cuffs, which measure the oscillations from the blood vessel wall during cuff deflation, estimate systolic BP, diastolic BP, and mean arterial pressure (MAP). MAP is directly influenced by CO and SVR and is the preferred metric for targeting adequate end organ perfusion. In addition, BP measurement yields pulse pressure (PP), or the difference between systolic and diastolic BP, which may help discriminate between different forms of shock. A narrow PP (<20 mm Hg) may manifest due to diminished stroke volume (SV) and elevated SVR, as may be seen in cardiogenic shock. A widened PP (>40 mm Hg) may manifest in patients with reduced SVR and a compensatory increase in SV, as seen in septic shock.

PULSE PRESSURE AND STROKE VOLUME VARIATION ANALYSIS

PP and SV variation analysis are advanced noninvasive means to assess cardiovascular hemodynamics, including estimation of SV, CO, and fluid responsiveness. *Volume responsiveness* is usually defined as a greater than 10% to 20% increase (or variation) in PP or SV in response to increased cardiac preload. For example,

patients not responsive to preload changes, such as those experiencing cyclical increases in intrathoracic pressure from mechanical ventilation or increased venous return following passive leg raise, will demonstrate minimal (<10%) changes in the PP and SV. Several different noninvasive devices leverage this concept, including the Starling Fluid Management Monitoring System (Baxter International Inc), which measures thoracic bioreactance, and LiDCO (LIDCO Ltd), which analyzes beat-to-beat BP with an oscillometric cuff.

POINT-OF-CARE ULTRASOUND

Point-of-care ultrasound (POCUS) is an indispensable tool for characterizing and monitoring cardiovascular hemodynamics in patients who are in shock. A limited echocardiographic examination can be used to quickly gauge biventricular size and systolic function or to identify other structural abnormalities (eg, large pericardial effusion) that may explain shock. For operators with more advanced echocardiographic skills, an evaluation of diastolic function may help identify elevated left-sided filling pressures. In addition, lung ultrasound can quickly disclose extravascular lung water with the identification of sonographic B lines due to cardiogenic pulmonary edema.

POCUS may be used to estimate central venous pressure (CVP) by evaluating the inferior vena cava (IVC) size and inspiratory collapse, which is directly influenced by the patient's right atrial (RA) pressure and volume status. However, CVP estimation is not a wholly reliable means of estimating a patient's volume status, as IVC may be affected by a wide variety of conditions, including right ventricular (RV) heart failure, valvular heart disease (eg, tricuspid regurgitation), cardiac tamponade, pneumothorax, and positive pressure ventilation.

In addition, POCUS may be used to roughly estimate SV by measuring the left ventricular outflow tract (LVOT) volume-time integral (VTI) by pulse wave Doppler. Patients with a normal SV typically have LVOT VTI values greater than 20 cm. LVOT VTI

measurements may also be used to calculate SV if cross-sectional area (CSA) of the LVOT is known using the following equation: SV = LVOT VTI × $LVOT_{CSA}$. CO is then derived by multiplying the SV by the heart rate. Lastly, similar to SV variation analysis, cyclical changes to LVOT VTI can be used to assess fluid responsiveness in response to fluid administration or passive leg-raise maneuver.

Invasive Hemodynamic Tools and Methods

ARTERIAL LINES

Arterial catheterization enables continuous BP monitoring in an intensive care setting. Beyond continuous BP measurements, arterial lines can be linked to novel CO monitoring devices (eg, FloTrac/Vigileo device) that use arterial waveform–based pulse contour analysis to estimate SV, SV variation, and CO.

CENTRAL VENOUS CATHETERS

Central venous catheters (CVCs) permit direct CVP measurements, which, in turn, reflect the patient's RA pressure (when placed in the internal jugular or subclavian veins). In addition, CVP waveform characteristics can assist in identifying cardiac pathologies responsible for shock (eg, absent y descent in cardiac tamponade). Furthermore, measurement of central venous hemoglobin saturation ($ScVO_2$) can help identify abnormalities in global oxygen delivery and/or consumption. If the global transport of oxygen does not fully meet the metabolic demands of the body (eg, hemorrhagic or cardiogenic shock), an abnormally low $ScVO_2$ will be present. On the other hand, if global oxygen transport exceeds the metabolic needs of the body (eg, early septic shock), or if oxygen consumption is impaired, an elevated $ScVO_2$ will result.

SWAN-GANZ CATHETERS

Swan-Ganz catheters (SGCs) enable the measurement and derivation of a multitude of hemodynamic parameters (Table 87.1) that may provide valuable insights into patients' underlying hemodynamics. SGCs are uniquely equipped to directly measure RA pressure, pulmonary artery pressures (systolic, diastolic, and mean [mPA]), and pulmonary capillary wedge pressure (PCWP). Moreover, SGCs distinctively permit an estimation of CO, derived by either thermodilution or Fick methods, which can help differentiate the type of shock present. Serial CO measurements can also help clinicians identify and evaluate hemodynamic changes, including therapeutic responses to medical intervention(s).

TABLE 87.1 Swan-Ganz Catheter Parameters and Clinical Utility

Directly Measured	Formula	Normal Values	Clinical Utility
Right atrial pressure (RAP)	—	Mean 0-7 mm Hg	Right-sided filling pressures, evaluation of valvular disease (large V wave in TR)
Right ventricular (RV) pressure		Systolic 15-30 mm Hg, diastolic 1-7 mm Hg	Indicator of RV performance
Pulmonary artery pressure (PAP)	—	Systolic 15-30 mm Hg, diastolic 4-12 mm Hg	Evaluation of PH
Pulmonary capillary wedge pressure (PCWP)	—	Mean 4-12 mm Hg	Left-sided filling pressures, evaluation of valvular disease (large V wave in MR)
Calculated			
Cardiac output (CO)	$\text{Fick CO} = \frac{\text{Oxygen consumption}}{(\text{Arterial } O_2 - \text{Venous } O_2)}$ Thermodilution CO: cold fluid is injected and time to temperature change (washout) is measured. Higher CO causes quicker washout.	4-8 L/min	Indicator of LV performance and oxygen delivery to peripheral tissues, helps characterize shock (cardiogenic vs other), monitor response to inotropes and/or afterload reduction
Cardiac index (CI)	$\frac{\text{CO}}{\text{Body surface area}}$	2.5-4 L/min/m^2	

Derived			
Systemic vascular resistance (SVR)	$SVR = \frac{MAP - CVP}{CO}$	700-1,600 dynes-sec/cm^{-5}	Helps characterize shock (cardiogenic vs septic), monitor response to vasodilators, pressors
Pulmonary vascular resistance (PVR)	$PVR = \frac{Mean\ PAP - PCWP}{CO}$	100-300 dynes-sec/cm^{-5}	Helps differentiate cause of PH in conjunction with PCWP (pre- vs postcapillary)
Pulmonary artery pulsatility index (PAPi)	$PAPi = \frac{Systolic\ PAP - Diastolic\ PAP}{RAP}$	Not established in general population, >4.8 associated with fewest adverse events in diverse population with cardiovascular disease	Indicator of RV function, PAPi <3.7 and <1.4 associated with worse outcomes in patients with PH and ambulatory HF, respectively; <1 indicates severe RV failure
Aortic pulsatility index (API)	$API = \frac{Systolic\ BP - Diastolic\ BP}{PCWP}$	Not established in general population, >2.9 associated with fewer adverse events in patients with HF	Incorporates LV output and filling pressure, low API (<1.45) prognostic for escalation of care or mortality in cardiogenic shock
Cardiac power output (CPO)	$CPO = \frac{MAP \times CO}{451}$	>1	Indicator of LV hydraulic energy output, low CPO (<0.6) prognostic for mortality in cardiogenic shock

HF, heart failure; LV, left ventricle; MR, mitral regurgitation; PH, pulmonary hypertension; TR, tricuspid regurgitation.

The Frank-Starling Mechanism

The Frank-Starling (FS) mechanism offers a helpful framework for hemodynamic assessment and monitoring. FS curves depict the relationship between cardiac preload (or end-diastolic pressure) and SV (Figure 87.1). In this relationship, increased preload translates into increased SV, as increased myocardial fiber stretch causes an increase in contractile force. This relationship persists until increasing ventricular loading finally gives way to diminishing SV due to excessive myocardial stretch. Conversely, if ventricular preload is decreased, SV may diminish. In addition, FS curves can also help portray the complex relationship between the heart's inotropic capacity and cardiac afterload (Figure 87.2). An increase in inotropy will shift the FS leftward and upward, while a decrease in inotropy will shift the FS rightward and downward. Similarly, decreased afterload will shift the FS leftward and upward, while increased afterload will shift the FS rightward and downward.

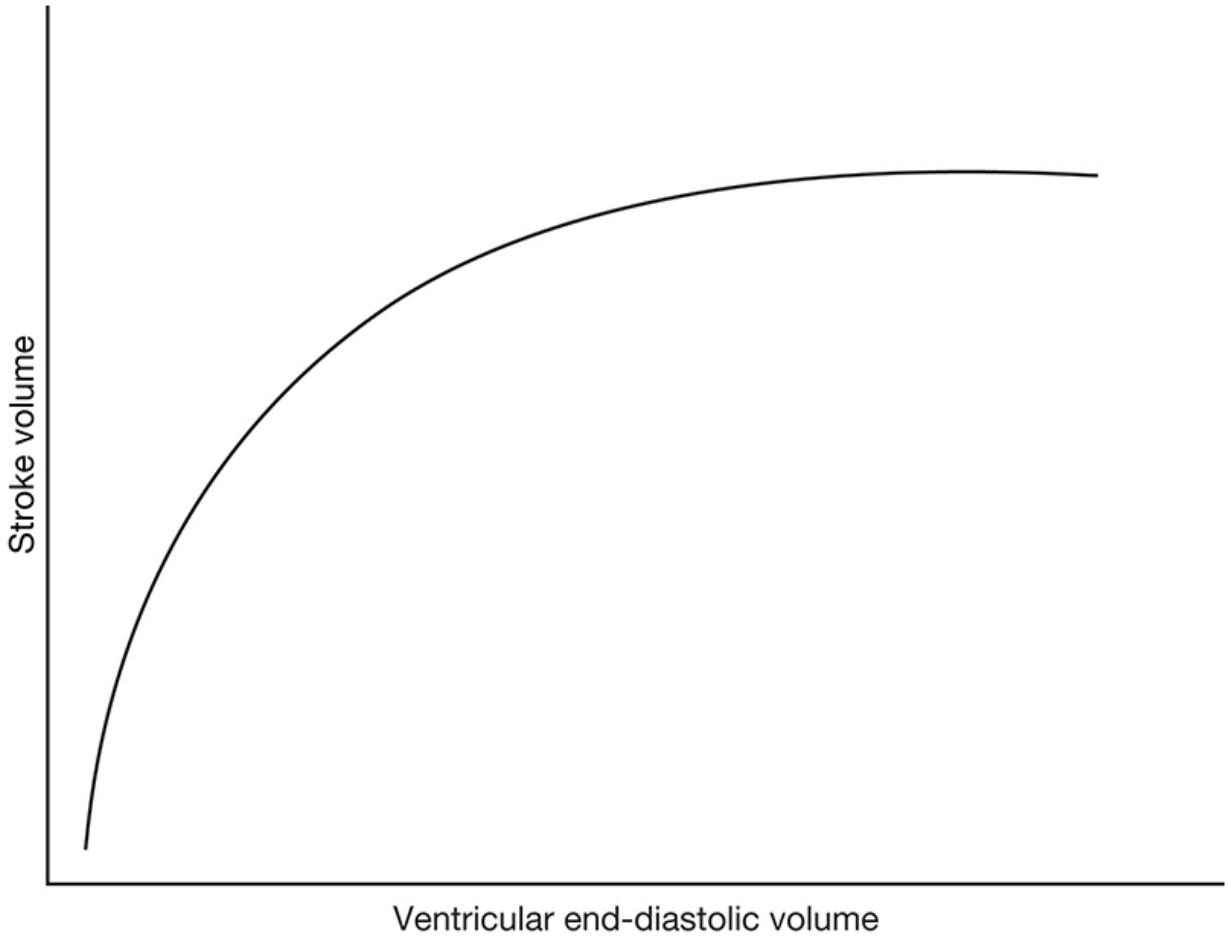


FIGURE 87.1 **A Frank-Starling curve depicting the relationship between cardiac preload (or end-diastolic pressure) and stroke volume.**

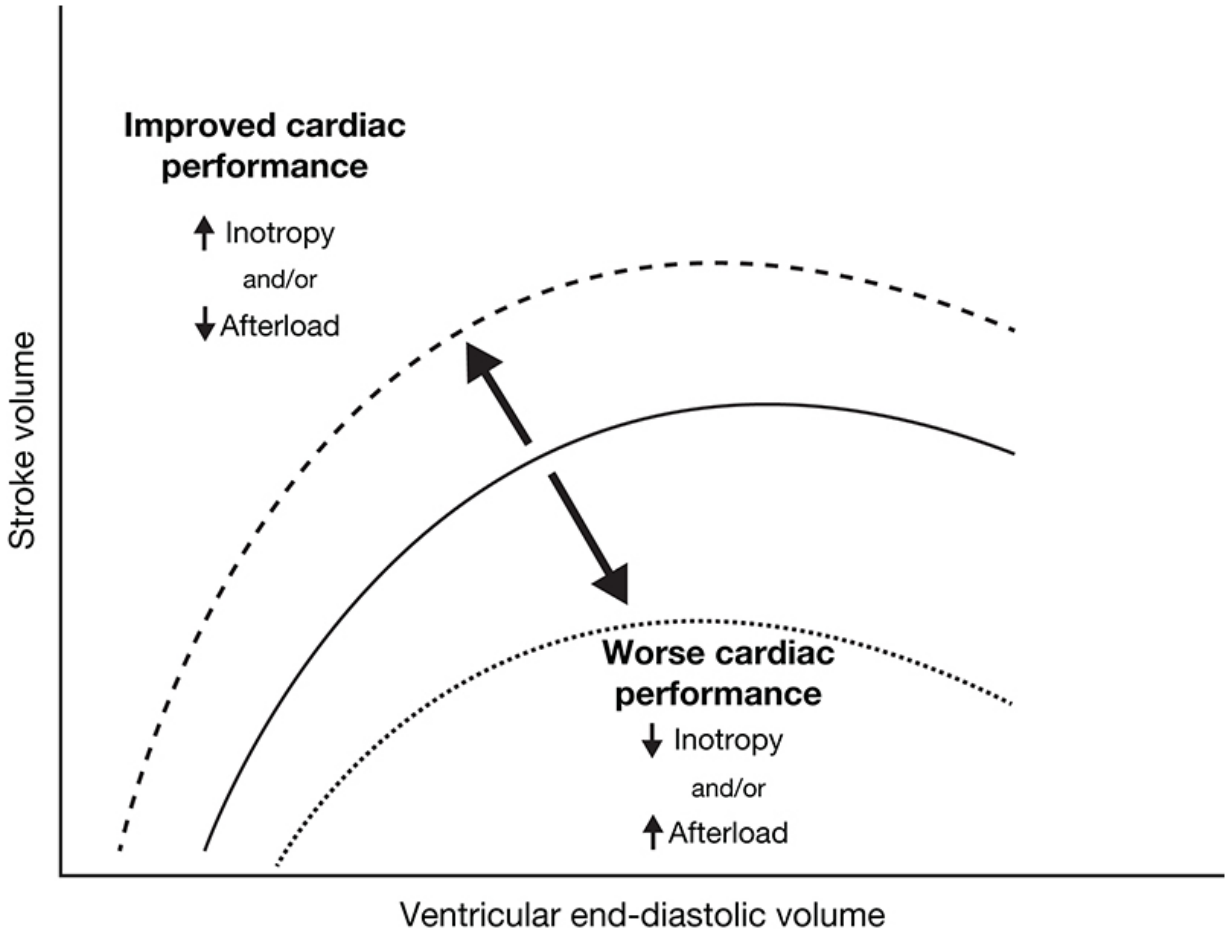


FIGURE 87.2 **Changes in the Frank-Starling curve occur with changes in inotropy and afterload: increased inotropy or decreased afterload shifts the curve leftward and upward, while a decrease in inotropy or increased afterload shifts the curve rightward and downward.**

Hemodynamic Profiles of Shock

HEMORRHAGIC OR HYPOVOLEMIC SHOCK

In hemorrhagic or hypovolemic shock, diminished cardiac preload translates into lower SVs, while the characteristics of the FS curve remain mostly unchanged (Figure 87.3).

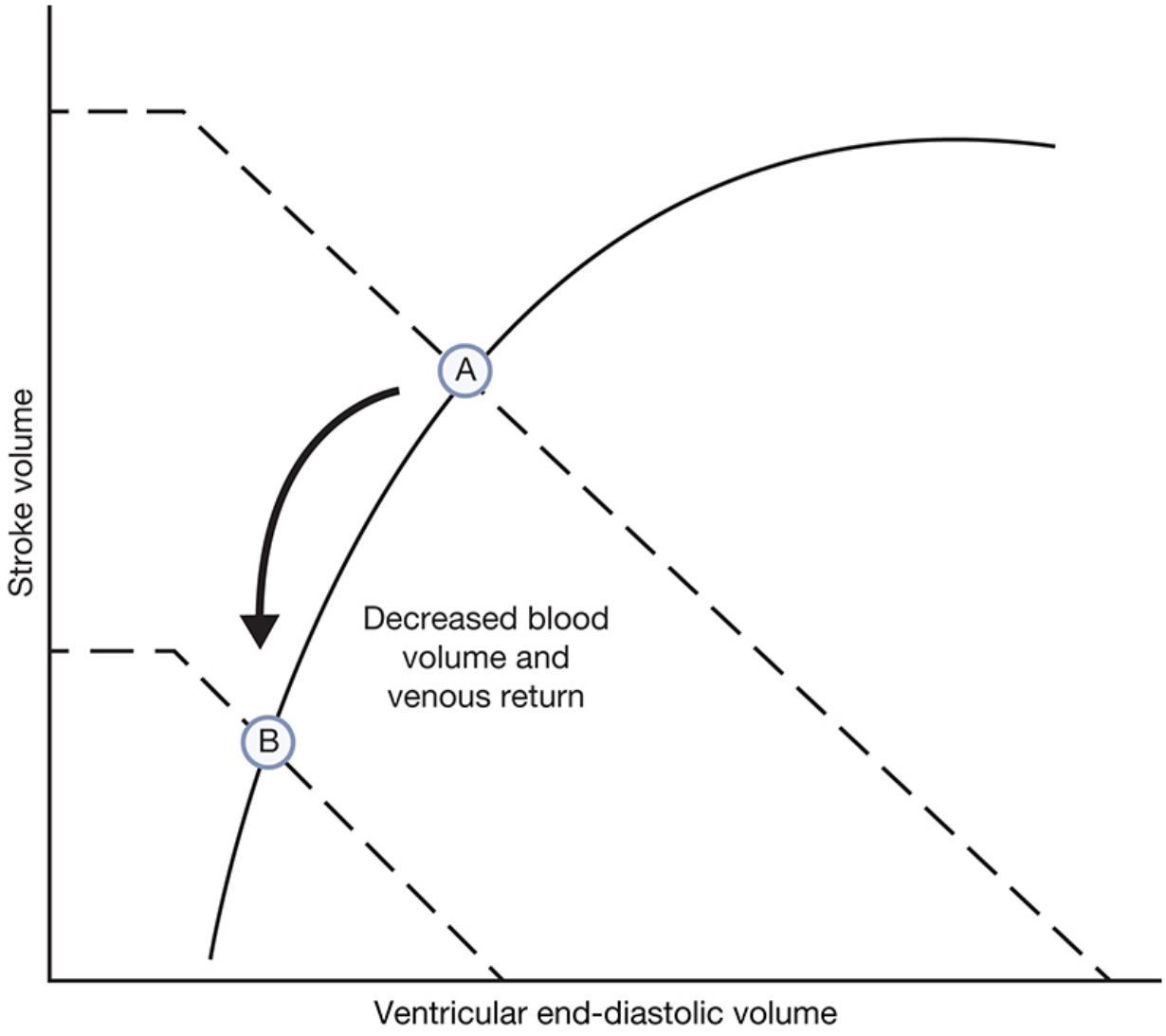


FIGURE 87.3 **In hemorrhagic or hypovolemic shock, decreased cardiac preload (represented by moving from point A to point B on the Frank-Starling [FS] curve) causes reduced stroke volume, while the characteristics of the FS curve remain unchanged.**

CARDIOGENIC SHOCK

In cardiogenic shock, the FS curve is positioned rightward and downward due to coexisting myocardial dysfunction and a compensatory increase in SVR (Figure 87.4). Thus, patients with cardiogenic shock simultaneously demonstrate diminished SV and elevated filling pressures. Remarkably, though patients with

cardiogenic shock are at high risk of adverse effects from elevated filling pressures (eg, acute pulmonary edema), they must maintain higher than normal intracardiac filling pressures to maintain SV. Thus, patients with cardiogenic shock are more dependent on preload and are especially vulnerable to volume shifts.

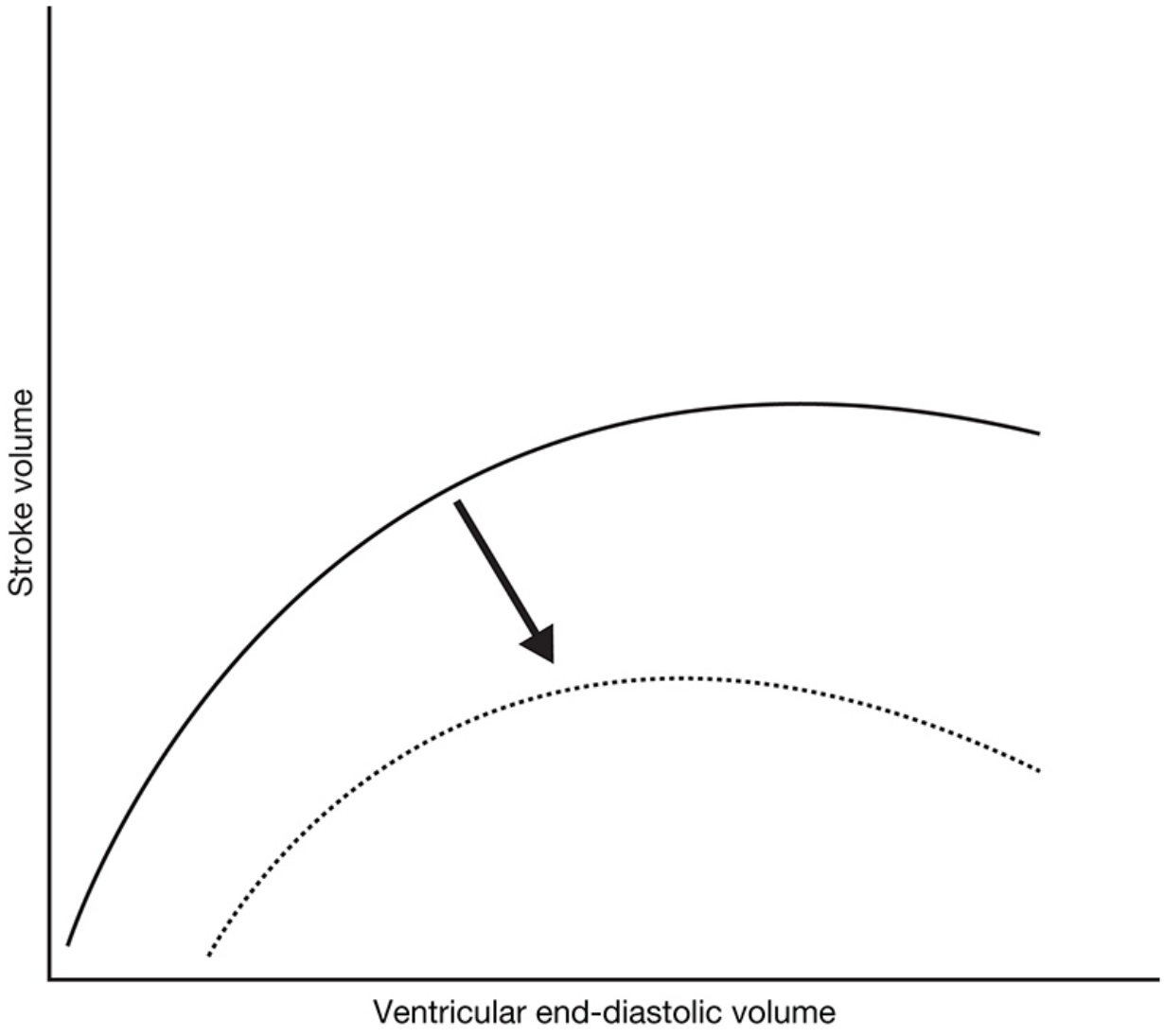


FIGURE 87.4 **In cardiogenic shock, myocardial dysfunction and a compensatory increase in systemic vascular resistance drive the Frank-Starling curve downward and rightward.**

SEPTIC SHOCK

In septic shock, a complex combination of hemodynamic forces may be present. Therefore, characterizing the overall hemodynamic effects of septic shock on any given patient can be challenging (Figure 87.5). Simultaneous arteriolar vasodilation and surge in cardiac contractility would be expected to shift the FS curve leftward; however, this response may be countered by coexisting myocardial depression that shifts the FS curve rightward. Furthermore, the inflammatory state of septic shock may result in global vasodilation and capillary leak that reduces venous return and cardiac preloading.

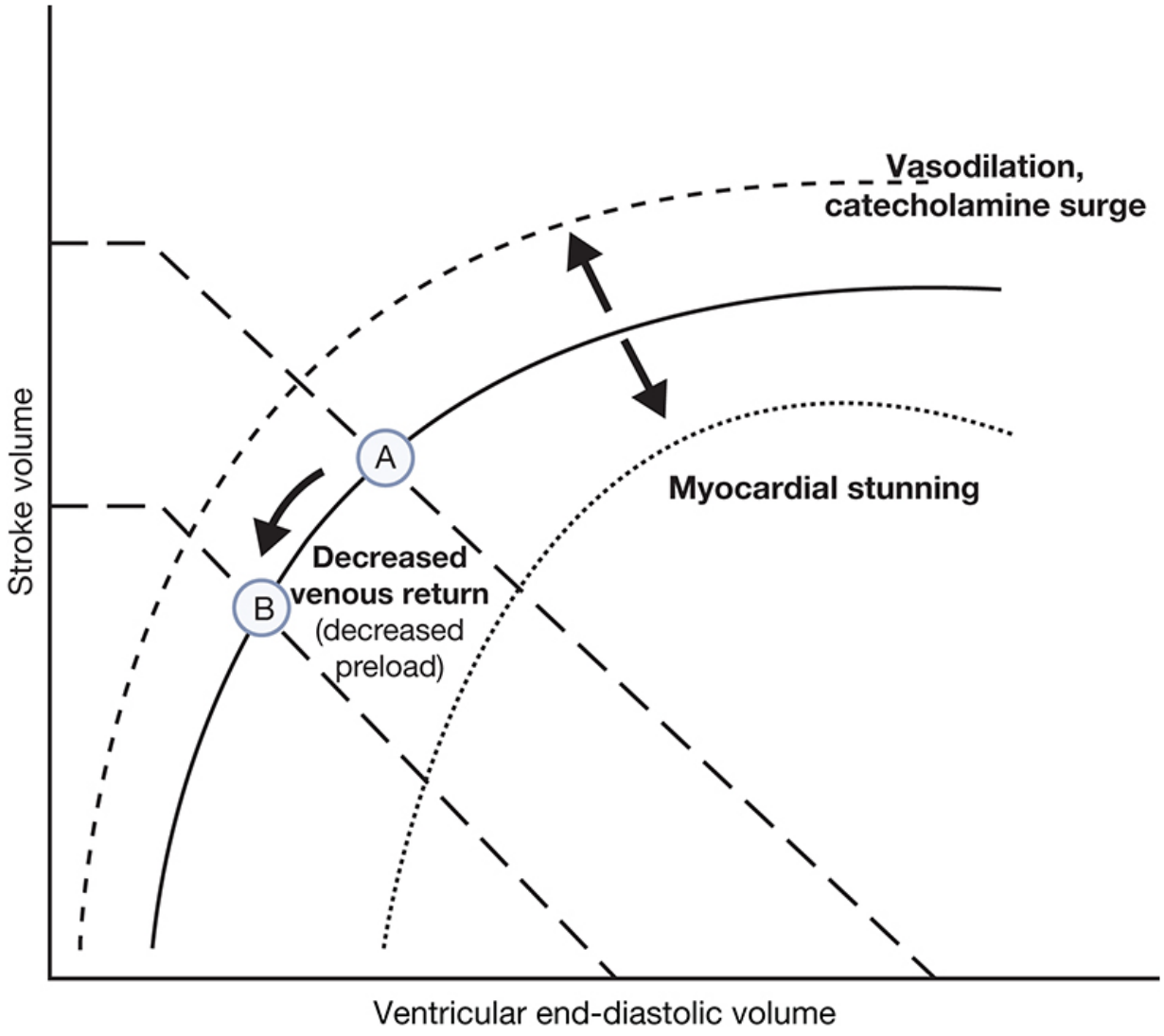


FIGURE 87.5 **In septic shock, competing hemodynamic forces can alter the Frank-Starling curve with an unpredictable net effect:**

vasodilation and catecholamine release increase inotropy and push the curve leftward, while systemic inflammation in septic shock may diminish inotropy, pushing the curve rightward. Vasodilation may also reduce cardiac preload (represented as a change from point A to point B along the Frank-Starling curve).

MIXED SHOCK

In general, mixed shock represents a combination of impaired cardiac performance and systemic vasodilation. Mixed shock is commonly seen in patients with advanced cardiac disease who develop sepsis, or patients with cardiogenic shock who later develop vasodilation triggered by inflammatory cytokines. In such cases, it is often unclear to what extent cardiac failure and vasodilation are contributing to a low MAP. Thus, invasive hemodynamic monitoring tools may be especially helpful in clarifying their relative contributions. $ScVO_2$ measurements, for example, may help detect deficits in CO. Alternatively, SVR calculations may help determine whether arteriolar vasodilation is an important contributor to a low MAP.

COEXISTING ENDOGENOUS AND EXOGENOUS FORCES

Lastly, all patients with shock, irrespective of the underlying etiology, have an unmeasurable and varying contribution of endogenous compensatory responses (eg, catecholamine release) and other detrimental factors (eg, inflammatory cytokine release) that may influence their overall hemodynamic state. Furthermore, a wide variety of commonly encountered external factors can greatly influence a patient's hemodynamics. For example, positive end-expiratory pressure delivered by mechanical ventilation may decrease RV preload and increase RV afterload and thereby impair CO. In addition, negative inotropic agents (eg, beta-blockers) can directly impair CO and blunt compensatory responses to shock. Lastly, sedating medications, which can simultaneously impair RV

preloading and lower SVR by globally reducing vascular tone, can have profound detrimental effects on CO and MAP.

Hemodynamics in the Treatment of Shock

HEMORRHAGIC OR HYPOVOLEMIC SHOCK

In hemorrhagic or hypovolemic shock, the most efficacious and direct means of correction is administration of intravenous fluids (eg, crystalloids or blood products), with the goal of increasing cardiac preload, which will, in turn, increase SV and thereby improve MAP. Although vasopressor agents in this setting will increase MAP, this intervention will not address the underlying insult and may translate into impaired CO due to higher cardiac afterload.

CARDIOGENIC SHOCK

To improve hemodynamics in cardiogenic shock, one aim is to shift the FS curve leftward and upward through afterload reduction and/or inotropic support. In this way, SV can be increased, and end-diastolic pressure decreased. However, if these interventions do not, or are not expected to, sufficiently address a low MAP, alternative interventions, including vasopressors or mechanical circulatory support, may be necessary. Furthermore, judicious fluid administration may be helpful in select circumstances where cardiac preload is insufficient to maintain adequate SV (such as when the patient is on the leftmost portion of the FS curve).

Therapeutic interventions to address cardiogenic shock may have unintended adverse effects, especially when applied outside the desired clinical context. For example, excessive volume removal may dramatically impair CO, even to the point of hemodynamic collapse, because the heart is more preload dependent and requires higher filling pressures to maintain SV. Afterload reduction, especially in the setting of reduced MAP and low intracardiac filling pressures, may greatly reduce MAP by simultaneously lowering

cardiac preload and SVR. Vasopressor agents, although they advantageously increase MAP to salvage end-organ function (including the heart via coronary perfusion), also increase cardiac afterload, which may further impair CO. Lastly, inotropes may sometimes paradoxically impair cardiac performance by precipitating myocardial ischemia, dynamic LVOT obstruction, or cardiac arrhythmias.

SEPTIC SHOCK

Intravenous fluid resuscitation and vasopressors are cornerstone treatments for septic shock. Vasopressors directly increase SVR through arteriolar vasoconstriction and indirectly increase cardiac preload by venoconstriction. Fluid administration increases cardiac preload, which, in turn, augments CO. However, not all patients with septic shock will respond favorably to fluid administration (Figure 87.6). If too much fluid is provided, adverse effects from volume overload may result. Therefore, an assessment of responsiveness prior to intravenous fluid administration may be appropriate, especially in the later phases of treatment. Lastly, when coexisting cardiogenic shock is present, or when an insufficient increase in CO is identified, inotrope administration may be needed.

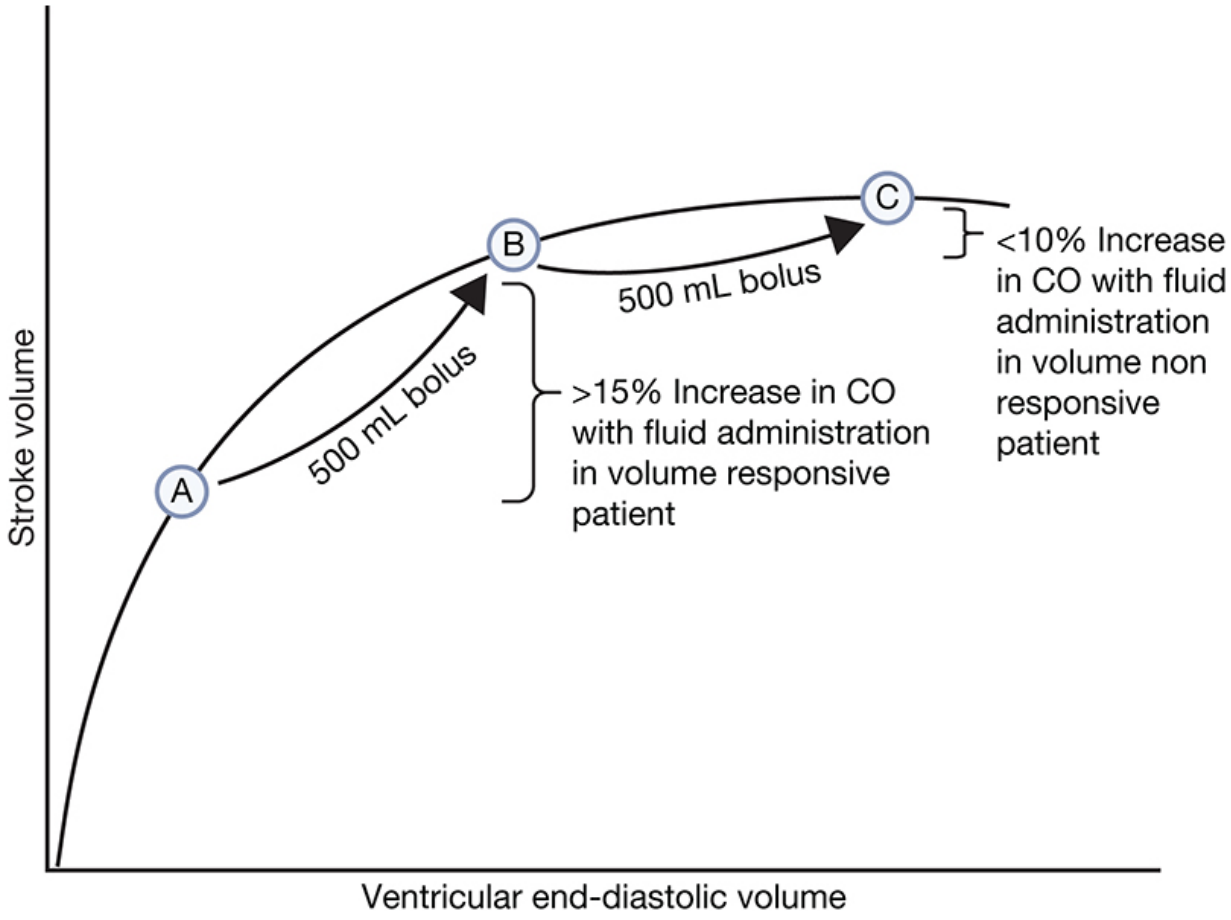

Stroke volume
A
B
C
500 mL bolus
500 mL bolus
>15% Increase in CO with fluid administration in volume responsive patient
<10% Increase in CO with fluid administration in volume non responsive patient
Ventricular end-diastolic volume

FIGURE 87.6 **Assessment of volume responsiveness may be used to determine whether additional preload with a fluid bolus is expected to improve stroke volume (move from point A to point B).** At a certain threshold, toward the right of the Frank-Starling curve, additional volume provides diminishing return with respect to improving cardiac output (CO) (move from point B to point C).

SUGGESTED READINGS

Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40(12):1795-1815.

Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med*. 2007;33(7):1125-1132.

88 Pericardiocentesis

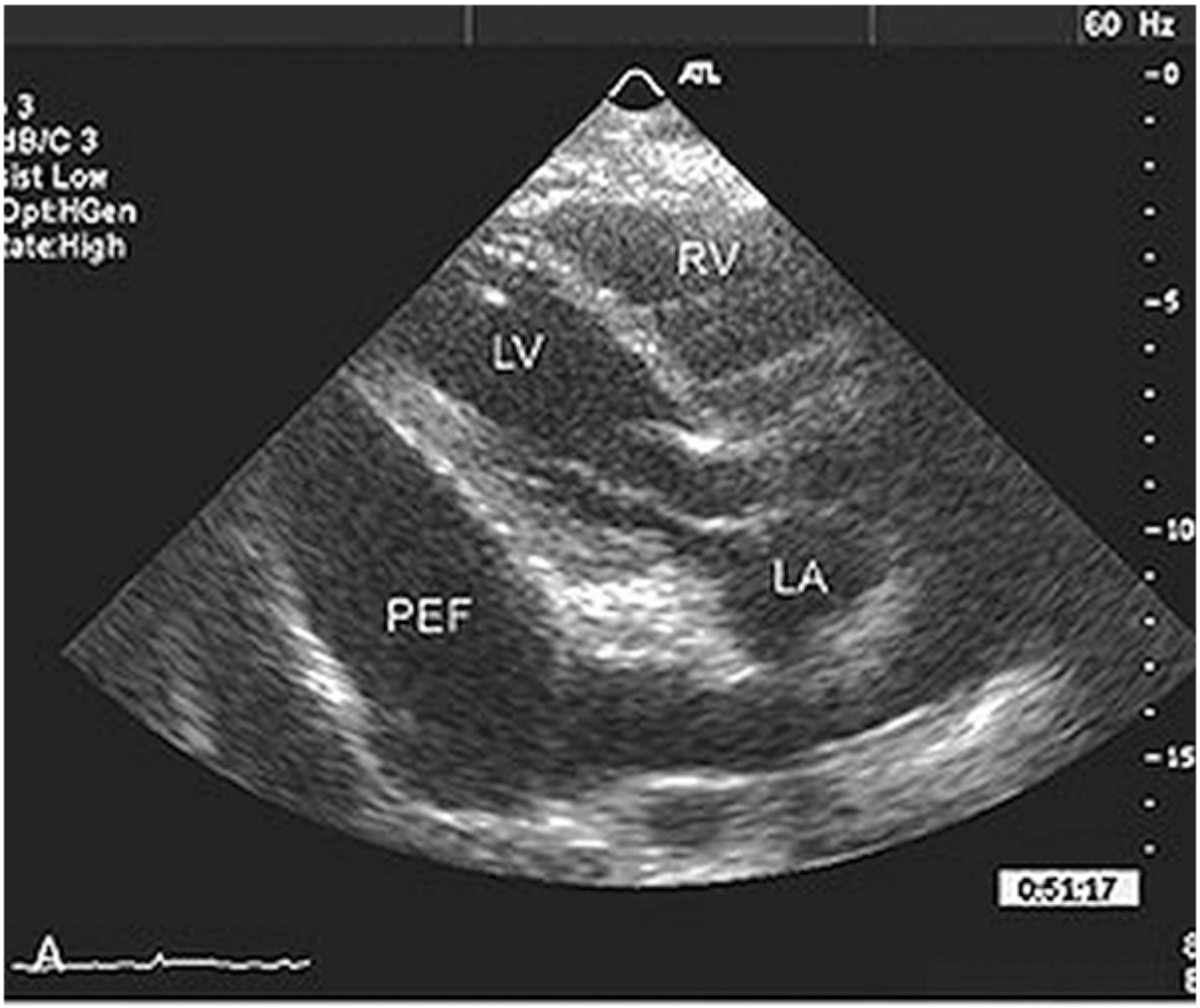
Bria D. Giacomino

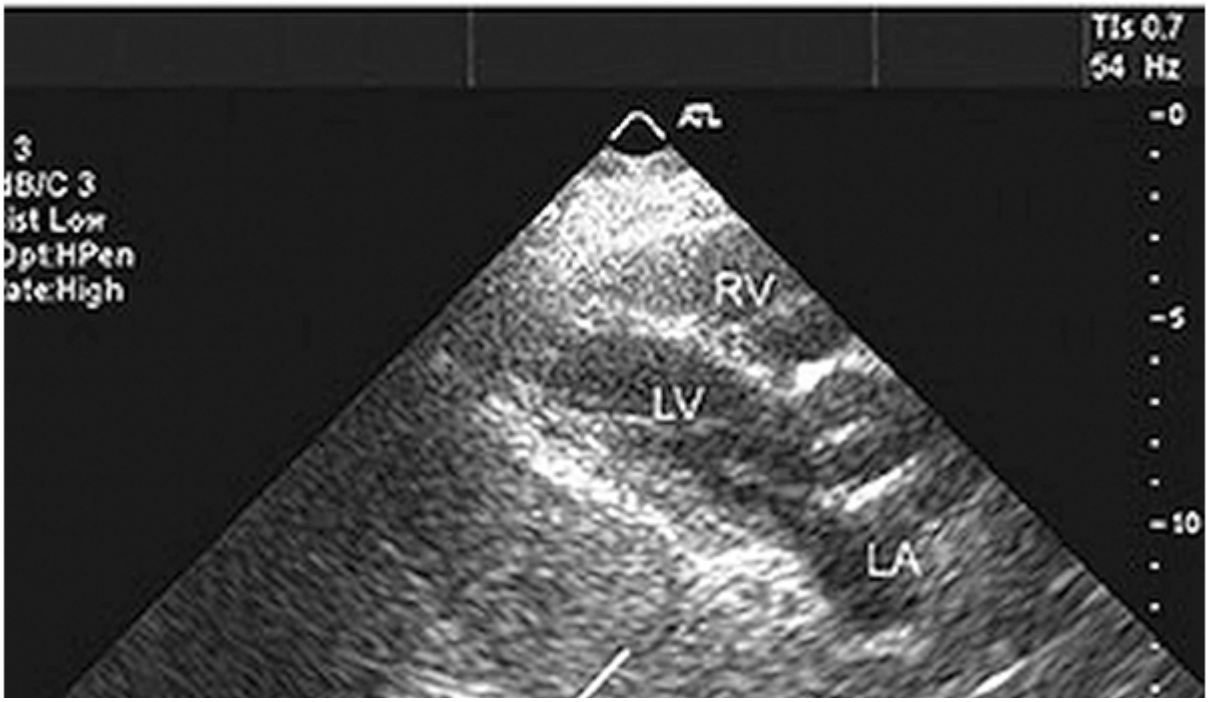
Pericardiocentesis is indicated in emergent settings by intensivists to treat severe cardiac tamponade with significant hemodynamic compromise, and more commonly by cardiologists as a diagnostic and/or therapeutic procedure for pericardial effusions. The procedure entails insertion of a needle into the pericardial sac, followed by insertion of a guidewire, successive dilations, and the placement of a pericardial drainage catheter. In the acute situation of cardiac tamponade, the fluid may be bloody, purulent, inflammatory, or rarely transudative. Ideally, to reduce the risk of complications, the procedure should be performed using real-time echocardiography or fluoroscopy. The overall risk of pericardiocentesis using echocardiographic guidance is less than 2% but increases to over 20% in emergent situations without echocardiography guidance. This chapter reviews the indications for immediate pericardiocentesis. Specifically, it reviews the situation of a patient in extremis, and outlines the key steps necessary for bedside fluid aspiration.

Pericardiocentesis should be considered and performed in the critical care setting to relieve hemodynamically significant cardiac tamponade. Cardiac tamponade is a condition in which fluid accumulates within the pericardial space. This fluid places external pressure on the myocardium and in the case of cardiac tamponade prevents filling of the cardiac chambers. It is clinically diagnosed, classically marked by hypotension, jugular venous distension, and muffled heart sounds, known as Beck triad. Hypotension and jugular venous distension are a result of decreased stroke volume and impaired venous return due to the pressure effect of fluid in the pericardial sac, while muffled heart sounds occur due to the acoustic effects of a large amount of fluid within the pericardial sac. Although the presence of all three elements of Beck triad is highly suggestive

of cardiac tamponade, only a small number of cases actually present with all these signs. Additional signs of tamponade include the presence of pulsus paradoxus (a decrease in systolic pressure >10 mm Hg during inspiration), as well as electrical alternans and low QRS voltage on electrocardiography.

Prior to proceeding with pericardiocentesis, it is recommended to perform a transthoracic echocardiogram to confirm the presence of an effusion and tamponade physiology. This allows for the identification of an ideal window for needle insertion. In postcardiac surgery patient, a transesophageal echocardiogram may be preferred because of the possibility of a loculated, posterior effusion (Figure 88.1). Additionally, postoperative bandages and wounds may limit adequate transthoracic imaging.


60 Hz
RV
LV
LA
PEF
0:51:17


TIs 0.7
54 Hz
RV
LV
LA

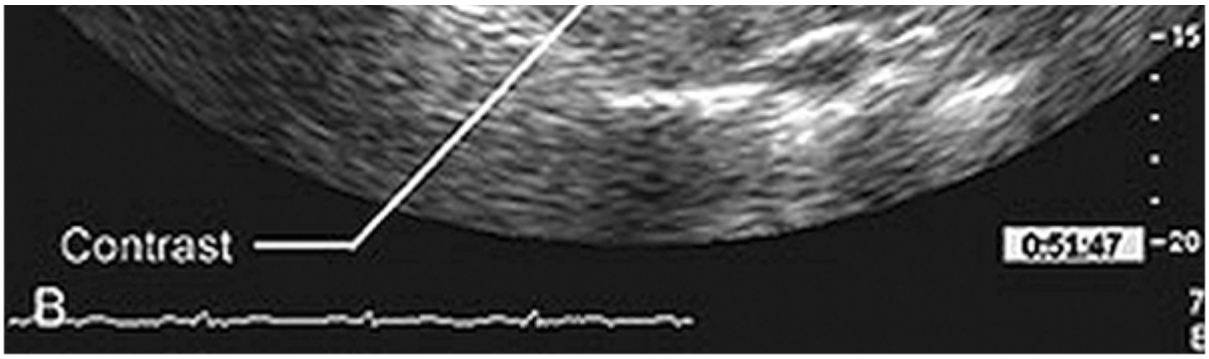


FIGURE 88.1 **Parasternal long-axis echocardiogram recorded in a patient with a large posterior pericardial effusion (PEF)**. Pericardiocentesis is being undertaken with echocardiographic guidance. **A:** There is a large posterior pericardial fluid collection. **B:** Agitated saline has been injected via the pericardiocentesis needle. There is now echo contrast in the previously clear pericardial space confirming that the pericardiocentesis needle is in the pericardium. LA, left atrium; LV, left ventricle; RV, right ventricle. (Reprinted with permission from Moscucci M. *Grossman & Baims Cardiac Catheterization, Angiography and Intervention*. 8th ed. Wolters Kluwer; 2013.)

The amount of fluid necessary to cause tamponade varies and depends more on the rapidity of fluid accumulation than the volume of fluid. In cases of malignant effusions, the fluid may collect gradually, stretching the pericardial sac to the point that it contains over 1 L of fluid before creating tamponade. In contrast, trauma may quickly lead to tamponade with only 100 to 200 mL of fluid or blood. A list of possible causes of cardiac tamponade in the intensive care unit (ICU) is found in Table 88.1. The most common cause of tamponade is malignancy. The decision to perform a bedside pericardiocentesis is based on hemodynamic instability and the development of obstructive shock. Intubation should be avoided if possible because of the risk of worsening the obstructive shock caused by tamponade, resulting from the change in intrathoracic pressure during and after intubation. Vasopressors have limited capacity to improve organ perfusion in this setting.

TABLE 88.1 Causes of Cardiac Tamponade in the Intensive Care Unit

Neoplasm
Infectious pericarditis (viral, bacterial, tubercular, parasitic)
Uremia
Postmyocardial infarction with ventricular rupture
Complication of a catheter-based procedure (pacemaker lead insertion, central line placement, or coronary catheterization)
Compressive hematoma after cardiothoracic surgery
Traumatic hemopericardium
Systemic autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis)
Aortic dissection
Drugs (hydralazine, procainamide, isoniazid, minoxidil, anticoagulation treatment)
Idiopathic

The safety of the procedure is dramatically improved when echocardiography guides needle placement and by the experience of the operator performing the procedure (Figure 88.2). Complications may include myocardial injury and laceration, ventricular perforation, coronary artery laceration, pneumothorax, ventricular arrhythmias, infection, peritoneal puncture, liver laceration, air embolism, injury to the stomach, vascular injury (internal mammary artery), failed drainage, and death. The incidence of such complications ranges from approximately 1.3% to 1.6% with transthoracic echocardiographic guidance, but can be as high as 20.9% without imaging guidance (Figure 88.3). Major complications such as ventricular rupture and death are rare.

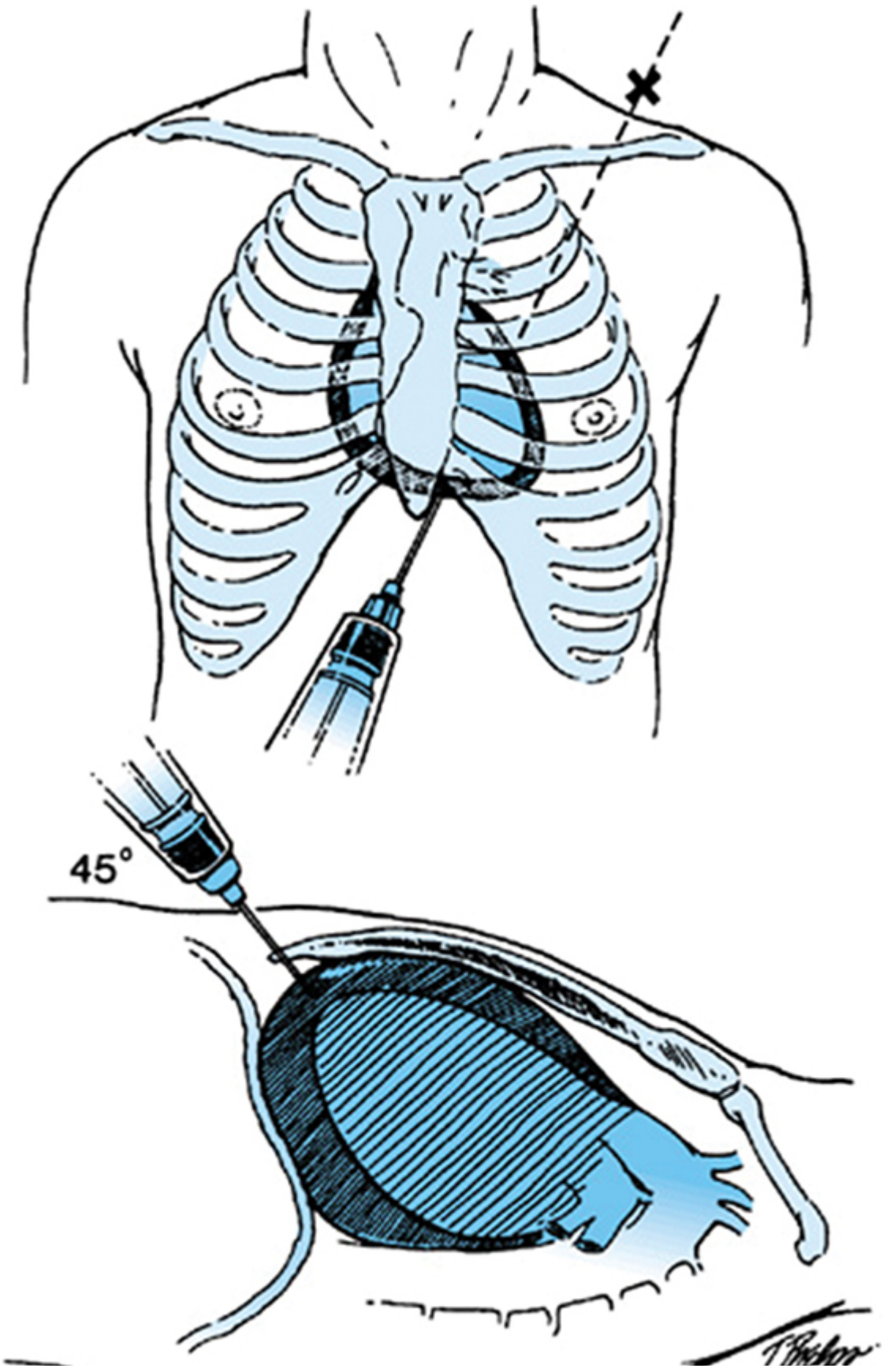

45°

FIGURE 88.2 **Pericardiocentesis**. (Reprinted with permission from Nichols DG, Yaster M, Lappe DG, Haller JA, eds. *Golden Hour: The Handbook of Pediatric Advanced Life Support*. 2nd ed. Yearbook; 1996.)

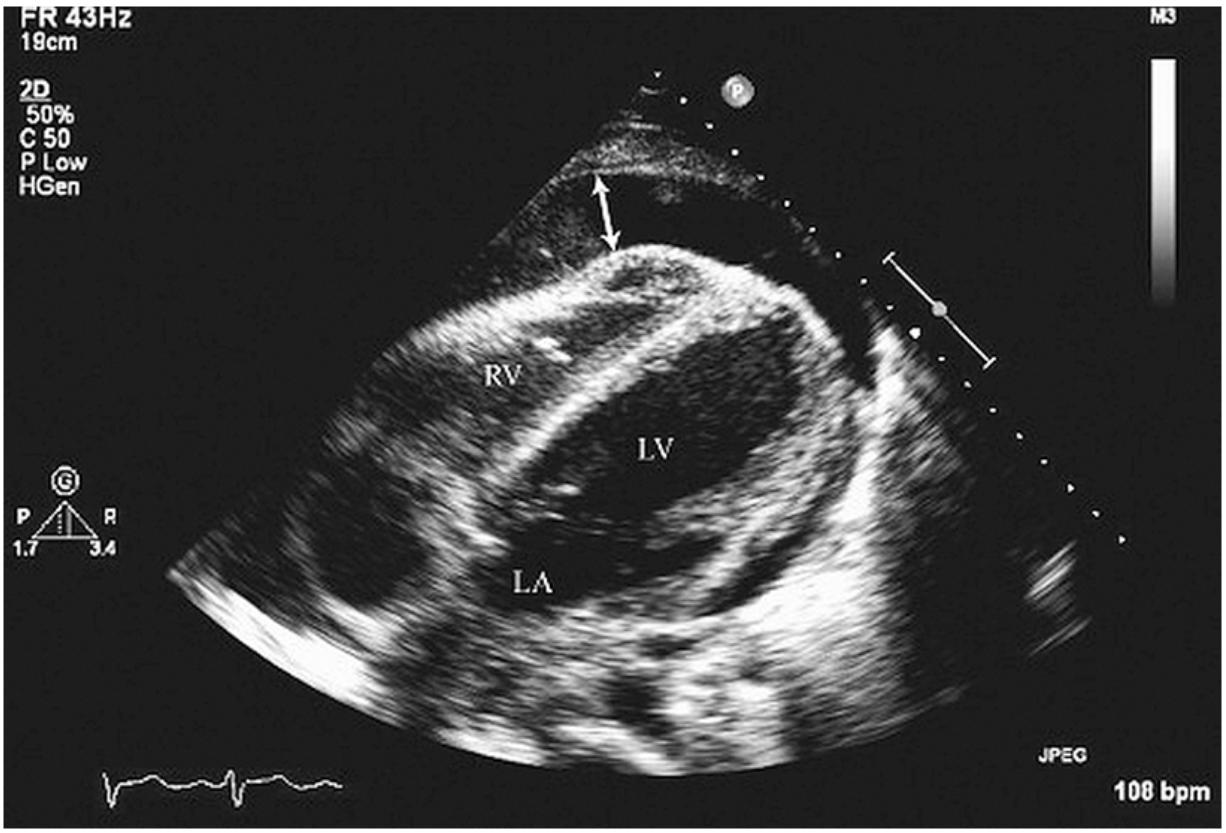


FIGURE 88.3 **Echocardiogram recorded from the subcostal position in a patient with a moderate pericardial effusion**. Note the approximate 1.5-cm distance between the pericardium and right ventricular free wall (*arrows*), implying a significant distance between the pericardium and the heart, which may confer a decreased risk of pericardiocentesis if approached from the subcostal position. (Reprinted with permission from Armstrong WF, Ryan T. *Feigenbaum's Echocardiography*. 7th ed. Wolters Kluwer; 2009.)

There are only a few relative contraindications for pericardiocentesis. These include coagulopathy (INR >1.4), recent use of direct oral anticoagulants that cannot be reversed,

thrombocytopenia (platelets <50,000), and small, posterior or loculated effusions. Acute aortic dissection with associated hemopericardium is known to be a major risk factor for increased perioperative mortality. Therefore, patients with cardiac tamponade complicating aortic dissection should undergo immediate surgical repair. While this condition has classically been identified as an absolute contraindication to pericardiocentesis due to concerns that rapid and aggressive drainage of the hemopericardium could lead to worsening leak from the aorta, recent data has demonstrated that careful and controlled drainage of hemopericardium can be an effective perioperative management strategy to temporize these patients. A surgical procedure such as subxiphoid pericardiostomy can be considered in cases where effusions are likely malignant and sufficient time is available (Figure 88.4). The surgical approach creates a pericardial window, allowing continued drainage of fluid into the peritoneum or thoracic cavity. Recent studies have shown similar recurrence rates of pericardial effusions when comparing pericardial windows to percutaneous pericardiocentesis with a catheter left in place for prolonged drainage, especially in malignant effusions. Therefore, repeat percutaneous pericardiocentesis is preferred over surgical pericardiostomy due to increased risks associated with the surgical procedure. The pericardial catheter drain is typically left in place for 24 to 48 hours, and removal should ideally be considered as the rate of fluid output diminishes to less than 25 to 30 mL per day. Malignant effusions may have higher rates of drainage and require longer duration of catheter placement. However, the risks of complications that can occur with increased duration of drain placement, especially infection, should be weighed against higher drain output. Removal can be considered when the rate of drain output decreases to less than 50 to 100 mL per day.

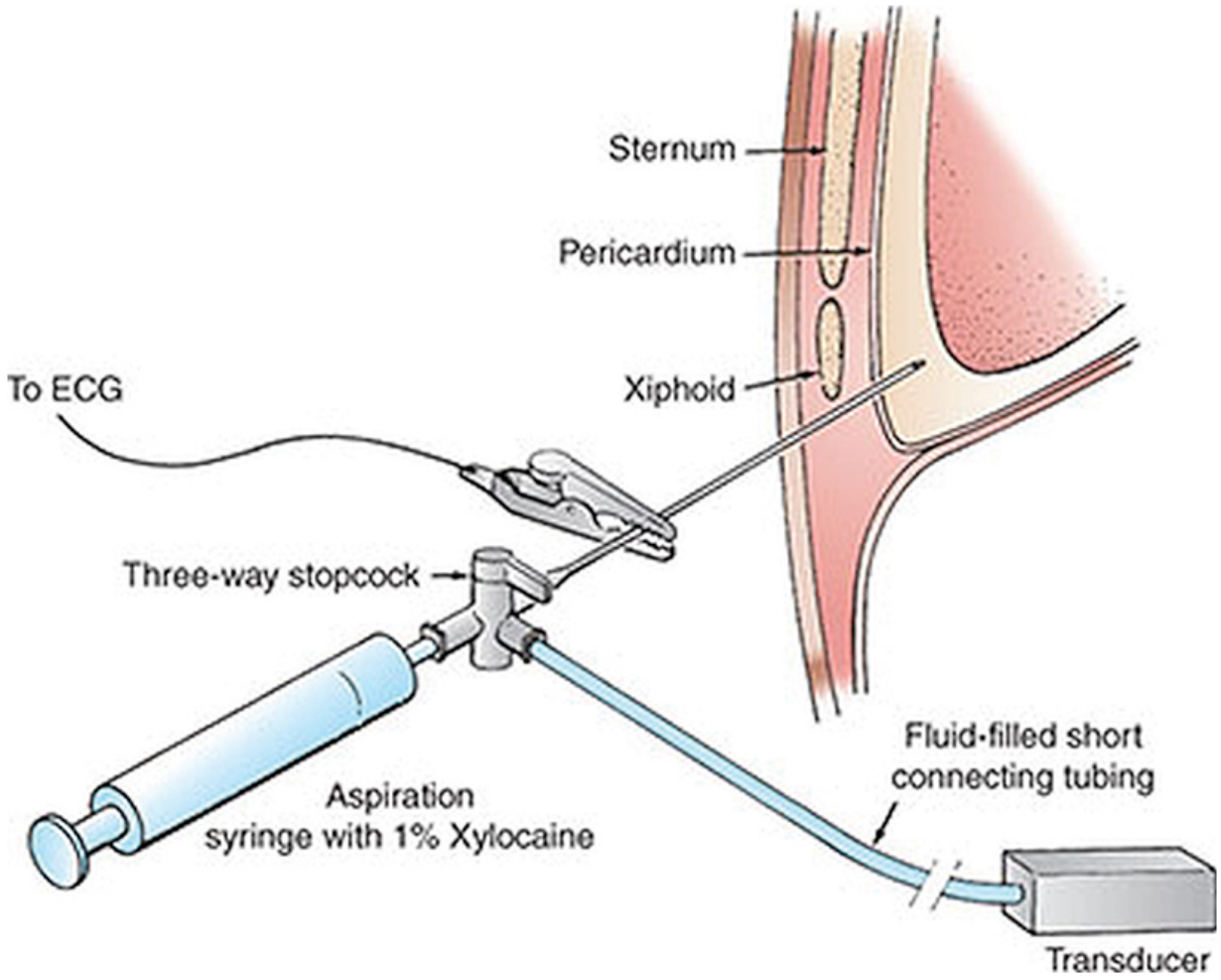


FIGURE 88.4 **Diagram showing the subxiphoid approach to pericardiocentesis with pressure and ST-segment monitoring**. A hollow, thin-walled, 18-gauge needle is connected via a three-way stopcock to an aspiration syringe filled with 1% Xylocaine and to a short length of fluid-filled tubing connected to a pressure transducer. A sterile V lead of an electrocardiographic recorder may be attached to the metal needle hub. The needle is advanced until pericardial fluid is aspirated or an injury current appears on the V-lead electrocardiographic recording. Once fluid is aspirated, the stopcock is turned so that needle-tip pressure is displayed against simultaneously measured right atrial pressure from a right heart catheter. When needle-tip position within the pericardial space is confirmed, a J-tipped guidewire is passed through the needle into the pericardial space, the needle is removed, and a catheter with end and side holes is advanced over the guidewire and subsequently connected via the three-way stopcock to both the transducer and the syringe. This permits, first, thorough drainage of the pericardial effusion using

a catheter rather than a sharp needle and, second, documentation that tamponade physiology is relieved when right atrial pressure falls, and intrapericardial pressure is restored to a level at or below 0. ECG, electrocardiogram. (Reprinted with permission from Moscucci M. *Grossman & Baims Cardiac Catheterization, Angiography and Intervention*. 8th ed. Wolters Kluwer; 2013.)

The following steps outline the procedure, which is ideally performed with real-time ultrasound guidance.

Steps for Bedside Pericardiocentesis

1. *Gather the necessary equipment*, which is available at most centers in a pre-packaged pericardiocentesis kit. Equipment includes, but is not limited to:
   a. Antiseptic (betadine or chlorhexidine gluconate)
   b. Local anesthetic (lidocaine 1%)
   c. Sterile drapes, gown, cap, and face mask
   d. Syringes, 20 and 60 mL
   e. Scalpel, no. 11
   f. Needles, 18 ga, 1.5 in; 25 ga, 5/8 in
   g. Spinal needle, 18 ga, 7.5 to 12 cm
   h. Guidewire
   i. Pericardiocentesis catheter
2. *Patient positioning:* Ensure the patient is on cardiac monitoring with supplemental oxygen. If time permits, decompress the stomach with a nasogastric tube. Place the head of the bed at a 45° angle to cause fluid collection inferiorly and bring the heart closer to the anterior chest wall.
3. *Identify insertion site:* Locate the patient's xiphoid process and left costal margin by palpation. The most common sites of needle insertion are marked by black dots below. When using

echocardiographic guidance, the ultrasound probe can identify the safest site for needle insertion. Generally, the subxiphoid site is preferred, but parasternal and apical approaches are also possible, depending on where the pericardial collection width is greatest.

4. *Prep site:* Use sterile technique with antiseptic solution, drapes, and anesthetize the skin with lidocaine if time allows.
5. *Needle insertion:* Begin by making a small incision at the insertion site with the scalpel. Fill the 20-mL syringe with 10 mL of sterile saline, evacuate the air, and attach to the 18-gauge needle. As the needle advances, place constant suction on the syringe. Stop to inject saline (0.5-1 mL) intermittently to prevent tissue from clogging the needle.
6. *Needle angle:* Advance the needle toward the left shoulder at a 30° to 45° angle to the abdominal wall. Slowly advance the needle past the posterior rib border of the left costal margin, then flatten it to a 15° angle.
7. *Needle advancement:* Continue advancing the needle until pericardial fluid is returned. ST-segment elevation or abrupt electrocardiogram (ECG) changes indicate myocardial injury. In this case, slowly withdraw the needle.
8. *Aspiration:* Remove the 20-mL syringe and replace with a larger syringe to continue aspirating as much fluid as possible. In shock due to tamponade, removal of as little as 50 mL of fluid can cause rapid improvement in cardiac output. If time is available and echocardiographic guidance is being utilized, inject agitated saline into the pericardial space to confirm the correct positioning of the needle tip prior to guidewire insertion. If a bloody aspirate is obtained, it can be injected into a dish and observed for clotting. Pericardial fluid with blood will often not clot, but blood aspirated from the ventricle will clot.
9. *Pericardial drain placement:* Pericardial drains help prevent reaccumulation of fluid in the next 1 to 2 days. First insert the guidewire found in the pericardiocentesis kit into the needle.

Remove the needle over the wire, keeping the wire in hand to avoid losing its place. Slide a 6- to 8-French dilator over the wire to form a tract. A larger skin incision may be needed to advance the dilator. Remove the dilator, then advance the drainage catheter over the guidewire into the pericardial space. Remove and discard the guidewire, leaving the catheter available for draining the effusion. Suture in place and cover with a sterile dressing. Fluid can be removed through a three-way stopcock until the patient is hemodynamically stable.

10. *Continued catheter drainage:* Two options for continued drainage of the pericardial fluid exist. The catheter may be directly connected to tubing and placed on a suction bulb, or the tubing can be left for gravity drainage. To maintain patency, flush the tubing with saline every 1 to 2 hours. Alternatively, fill the tubing and catheter with urokinase. In this case, open the tubing every 2 to 4 hours for a 1-hour drain.
11. *Diagnostic studies:* Depending on the clinical situation, several possible studies may be obtained. Send the fluid for cell count with differential, glucose, protein, Gram stain, culture (aerobic, anaerobic, acid fast bacilli [AFB]), lactate dehydrogenase (LDH), cytology, tumor markers, hematocrit, rheumatoid factor (RF), and antinuclear antibody (ANA).
12. Postprocedural chest x-ray (CXR) should be performed to evaluate the positioning of the drain and rule out a pneumothorax. A repeat transthoracic echocardiogram should reveal resolution of the effusion.

SUGGESTED READINGS

Fitch MT, Nicks BA, Pariyadath M, et al. Videos in clinical medicine. Emergency pericardiocentesis. *N Engl J Med.* 2012;366:e17.

Video presentation which covers the procedure in detail, including risks.

Gluer R, Murdoch D, Haqqani HM, et al. Pericardiocentesis—how to do it. *Heart Lung Circ.* 2015;24(6):621-625.

Thorough review of the procedure with excellent images.

89 Extracorporeal Life Support

Jon Greenberg

Extracorporeal life support (ECLS) represents an area of intense recent development in the care of critically ill patients. The technology has been around since the 1970s but has undergone significant evolution in its efficiency and application in recent years. A variety of modalities exist to provide various levels of support to patients with cardiac and/or respiratory failure. In this chapter, the discussion is on understanding the functionality and uses of ECLS, describing cannulation, determining which mode of support is necessary in a given clinical situation, appropriate patient selection, and reviewing the basic management of the patient on ECLS.

Extracorporeal Life Support Function

Four components comprise the basic ECLS circuit: a drainage cannula, a pump, an oxygenator, and a return cannula. Blood is removed from the body via a drainage cannula. The drainage cannula is connected to a pump, which propels the blood forward through an oxygenator where gas exchange occurs. The blood is then returned to the body through a separate return cannula.

The size, position, and configuration of cannulas for ECLS vary depending on the intended mode of support. There are two basic types of pumps currently used for ECLS, namely, roller-head pumps and centrifugal pumps. Roller-head pumps apply mechanical force to the tubing, propelling blood forward, similar to dialysis and apheresis machines. Centrifugal pumps, which are more commonly used due to improved durability and lower rates of hemolysis, utilize impellers that spin in a plastic casing and come into direct contact with the blood. These impellers are driven by a motorized magnet inside the

metal structure of the pump. The number of rotations per minute can be adjusted to optimize flow rates through the oxygenator, taking into consideration cannula size, volume status, and cardiac contractility, among other factors.

Various types of oxygenators are available for ECLS. Membrane oxygenators used in ECLS differ from those used in cardiopulmonary bypass as they lack a blood-air interface, do not pool blood, and, therefore, require lower levels of anticoagulation. In ECLS, oxygenators generally function by passing blood through hollow fibers, allowing for oxygenation and elimination of carbon dioxide (CO_2). CO_2 elimination in ECLS is highly efficient and is typically controlled by the “sweep speed,” or the speed of gas transfer through the oxygenator, which can be adjusted to optimize CO_2 elimination. Oxygen exchange, on the other hand, is less efficient and is primarily controlled by two variables: the rate of blood flow through the oxygenator and the fraction of delivered oxygen in the oxygenator (FDO_2). A blender on the oxygenator allows for the gas to be composed of different oxygen concentrations, ranging from 21% to 100% FDO_2, based on the clinical situation.

Multiple additional components can be added to the circuit depending on clinical need. In most circumstances, a device is used to flow the heated water through the oxygenator in a manner that maintains the temperature of the blood without actually having contact between the blood and the heated water. In the absence of such a device, the volume of blood outside the body (sometimes as much as 4-5 L/min) may be cooled to ambient temperatures.

Access sites along the cannula tubing can be included to facilitate blood draws or allow addition of a second extracorporeal device, such as continuous renal replacement therapy or apheresis. These access sites can be convenient but have the potential to increase the risk for clot formation owing to turbulence at the stopcock sites. These access points can also be sites of infectious contamination or entrainment of air into the circuit. Importantly, all access to the circuit must be located proximal to the oxygenator to allow for any entrained air or clots to be sent to the oxygenator rather than directly

into the patient's circulation. Pressure and saturation monitoring devices can also be attached at various points along the circuit to assist with clinical decision-making and mechanical optimization.

Cannulation

There are several ways that cannulation for ECLS can be performed. The most common locations within the hospital for cannulation are in the operating room and at bedside in the intensive care unit (ICU). Many institutions have developed transport ECLS programs where patients who are potentially too unstable for transport are cannulated on-site by a dedicated ECLS team and then transported on a circuit to the referral center for ongoing care. Cannulation teams vary from organization to organization but typically consist of a provider (or providers), an ECLS specialist (perfusionist, specialized nurse, etc), and a respiratory therapist, among others. The training background of the providers varies and can include cardiothoracic surgeons, general/trauma surgeons, intensivists, emergency physicians, and specially trained advanced practice providers (APPs).

The cannulation procedure for ECLS involves the insertion of two cannulas, which can be done using a surgical cut-down technique or percutaneously using Seldinger technique with serial dilations. Cannulas are placed into large central veins (such as the internal jugular vein, femoral vein, or subclavian vein) for venous cannula and, if necessary, into large arteries (such as the femoral/axillary artery or ascending aorta) for arterial cannula. Patients are often critically ill and heavily sedated prior to beginning the procedure. Regardless, the patient is prepped and draped in the usual sterile manner, close monitoring of vital signs is maintained throughout the procedure, and the patient is often adequately sedated prior to insertion of cannulas. The choice of cannulation site depends on the type of ECMO support needed, proceduralist preference, and the patient's condition. The venous cannula is usually inserted first and advanced into the vessel under fluoroscopic or ultrasound guidance until the desired position is reached, typically in the inferior vena

cava (IVC), right atrium, or right ventricle (RV), depending on the type of ECMO support needed. The cannula is then secured in place to prevent dislodgement during ECMO support. Next, the return cannula is inserted and advanced into the appropriate vessel under fluoroscopic or ultrasound guidance until the desired position is reached, typically in the superior vena cava (SVC) or aorta. The return cannula is also secured in place. Once both the cannulas are in place, they are connected in a “wet-to-wet” manner to the ECMO circuit to prevent leaks and to prevent air from being entrained into the circuit. Once the cannulas are secured in place and attached to the circuit, the flow is gradually increased to the desired level of support.

Extracorporeal Life Support Modes

ECLS comprises three distinct modes of support: venovenous extracorporeal membrane oxygenation (VV ECMO), venoarterial ECMO (VA ECMO), and extracorporeal CO_2 removal ($ECCO_2R$). Differences in support and indications for these modes are listed in Table 89.1. VA ECMO includes providing mechanical circulatory support in addition to gas exchange, VV ECMO provides gas exchange, and $ECCO_2R$ simply aids in CO_2 removal. There are several technical differences in the configuration of cannulas and equipment for these modes.

TABLE 89.1 ECLS Modes, Indications, and Differences in Support

ECLS Mode	Support Provided	Indications	Differences

ECLS Mode	Support Provided	Indications	Differences
VV ECMO	Gas exchange Respiratory support Oxygenation	Hypoxemic respiratory failure (after failing conventional measures and prone positioning) Hypercapnic respiratory failure (after failing conventional measures) Diffuse alveolar or pulmonary hemorrhage Severe bronchopleural fistula Status asthmaticus Inhalational injury Drowning Trauma Bridge to lung transplant Post–lung transplant for graft dysfunction Perioperative support for airway/lung operations Carbon monoxide poisoning	Flow rates up to 8 L/min Single cannula configurations emerging Does not provide hemodynamic support Can prevent lung injury in ARDS by allowing for lung rest
VA ECMO	Hemodynamic support Gas exchange Respiratory support	Cardiogenic shock Decompensated heart failure Massive pulmonary embolism Fulminant myocarditis Bridge to heart transplantation or ventricular assist device placement Postpartum cardiomyopathy Septic cardiomyopathy Acute drug overdose/intoxications Propofol infusion syndrome Trauma Hypothermia Inability to come off cardiopulmonary bypass postoperatively	Provides hemodynamic support and allows for end-organ perfusion Also provides respiratory support but to a lesser extent than VV ECMO Requires higher degree of anticoagulation Flow rates somewhat lower than VV ECMO

ECLS Mode	Support Provided	Indications	Differences
$ECCO_2R$	Carbon dioxide removal Minimal respiratory support	Hypercapnic respiratory failure (can be utilized to prevent intubation or shorten the course of mechanical ventilation)	Much lower flows Does not provide significant support for oxygenation Does not provide any hemodynamic support

ARDS, acute respiratory distress syndrome; $ECCO_2R$, extracorporeal CO_2 removal; ECLS, extracorporeal life support; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation.

Venovenous Extracorporeal Membrane Oxygenation

VV ECMO involves the use of larger cannulas and higher blood flow rates to provide support for oxygenation and CO_2 removal. The volume of blood flow that is necessary to achieve this goal is variable and depends largely on the size and intravascular volume status of the patient. Conventionally, a drainage cannula is positioned with its tip in the intrahepatic IVC via the femoral vein. This placement location is preferred to more distal locations on the basis of the relative collapsibility of positions lower in the IVC, which can compromise blood flow rates. A return cannula is generally placed in the right atrium via the internal jugular vein. Although relatively straightforward to place urgently in a patient who is critically ill, this cannulation strategy has a number of drawbacks. First, the proximity of the return cannula to the negative pressure generated at the tip of the drainage cannula can cause recirculation, a situation in which oxygenated blood is drained to the circuit prior to being circulated

through the body. This can be affected by the pump speed (and thus the degree of negative pressure at the drainage cannula tip), the volume status of the patient, and the proximity of the two cannulas to each other. In addition, patients are necessarily immobile as a result of the femoral cannulation site. There have been attempts at alternate sites of cannulation (such as the subclavian), but these come with their own issues. More recently, single-site, dual-lumen cannulas have been developed. These are slightly more technically difficult to place and often require fluoroscopic and/or echocardiographic guidance. The drainage lumen is positioned in the IVC, and the return lumen sits adjacent to the tricuspid valve, ideally with flow aimed directly into the RV. Transesophageal echocardiography during placement is often necessary to achieve this. These devices allow for greater mobility, although movement of the catheter can result in changes in flow and improper directionality of the return lumen. Regardless of cannulation strategy, the blood flow rate is occasionally insufficient to meet the oxygenation needs of the patient. Ensuring proper placement of the cannulas is essential, regardless of cannulation strategy, and point-of-care ultrasound (POCUS) is a valuable tool to help achieve this. Occasionally, alternative cannulation strategies, or even additional cannulas, may be required.

The pool of evidence regarding VV ECMO is significantly more robust, although there have been mixed data on its effectiveness in adult patients with respiratory failure. Early studies funded by the National Institutes of Health (NIH) in the 1970s failed to demonstrate a mortality benefit of ECLS in this context. Despite the skepticism following those studies, ECLS utilization continued over the ensuing decades. In particular, pediatric and neonatal applications drove advances in the technology of various components of the ECLS circuit. Changes in pump mechanics as well as the plastic composition of the circuit tubing and oxygenator membranes drastically impacted the tolerance, performance, and functionality of ECLS over this time frame.

The CESAR trial, published in 2009, demonstrated a mortality benefit associated with referral to a center with experience in the

provision of VV ECMO. While this was not, itself, a positive result for the impact of VV ECMO on these patients, it revived interest in the technology among many adult intensivists. The same year, the H1N1 influenza pandemic was associated with a substantial burden of disease and mortality, particularly among younger patients. This led to an increase in the utilization of VV ECMO in critically ill adults with severe respiratory failure. Another clinical trial compared VV ECMO and conventional treatment, which showed no mortality benefit but did show a number of secondary end points that improved with VV ECMO. Subsequently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID) pandemic provided additional opportunities to study the effectiveness of VV ECMO in patients with acute respiratory distress syndrome (ARDS). There have been multiple reviews and analyses of the data regarding patients with COVID who were placed on VV ECMO. The data have been difficult to fully analyze as there are multiple variables that are not able to be fully accounted for when parsing the data. At this time, it does appear that overall mortality for patients with COVID ARDS who were placed on VV ECMO increased as the pandemic progressed.

VV ECMO use has been widely reported in a variety of causes of the ARDS, including pulmonary contusions and ARDS following trauma, inhalation injuries, and drowning. Beyond ARDS, VV ECMO has also been studied in a number of other contexts. In particular, there are many reports of the use of ECLS to support patients awaiting lung transplantation. In addition, VV ECMO has been used in cases of status asthmaticus, severe pneumonia, pulmonary hypertension, pulmonary vasculitis and hemorrhage, exacerbations of chronic pulmonary diseases, and surgical airway reconstruction in patients who were unable to be otherwise supported during the procedure. The early results in these less frequently seen pathologies have been promising. Overall, the data regarding VV ECMO remain somewhat mixed, but the availability of this intervention is increasing as are the amount of centers comfortable utilizing it. This will lead to continued expansion of knowledge regarding multiple outcomes and how VV ECMO impacts them.

Venoarterial Extracorporeal Membrane Oxygenation

VA ECMO represents the most intensive level of extracorporeal support for cardiopulmonary function. Large cannulas are again used to generate sufficient blood flows to support oxygenation and CO_2 elimination. In VA ECMO, the return cannula is placed into the arterial system, which allows for hemodynamic support in patients with refractory shock. Cannulas are conventionally placed in the femoral vein and femoral artery, although there are many options for variability in this cannulation strategy. There is also the necessity to place a distal perfusion catheter into the femoral artery below the return cannula to avoid acute limb ischemia. In particular, the countercurrent return of oxygenated blood into the femoral artery does not always enable oxygenated blood return to reach the apex of the aortic arch or the ostia of the coronary arteries (colloquially known as *north/south syndrome*). One way to monitor for this possible complication is by placing an arterial line into the right radial artery as blood samples collected from this vessel will show a lack of adequate oxygenation in the event that a patient is developing north/south syndrome. In that event, oxygenated blood passes through the abdominal visceral and lower extremity circulation before returning to the heart, passing through the lungs, and ultimately reaching the coronary arteries, upper extremities, and brain. To correct this and allow for oxygenated blood return to directly reach these critical structures, the return cannula can be placed in the subclavian artery, which often requires a surgical cut-down and potential placement of an axillary graft. In addition, extra return cannulas can be placed in the venous system to allow oxygenated blood to return to the right side of the heart, assuming the RV has adequate function. Finally, in some patients, central VA ECMO is provided by utilizing a thoracotomy, or even sternotomy, to place cannulas in various positions within the heart and central vasculature. This allows for increased flows and cannula stability but is substantially more technically difficult and attended by significantly

higher rates of complication and morbidity. However, the cannulation strategy is structured, and the rate of blood flow can be adjusted to provide a variable degree of hemodynamic support. There is also the potential for the retrograde flow from the arterial cannula to be in opposition to anterograde flow out of the left ventricle (LV) as cardiac function improves, sometimes an assist device is placed to offload the LV and prevent this from occurring. Full-dose anticoagulation is also necessary in this context to prevent the development of clots in the arterial system, which can embolize critical structures and cause significant ischemic damage, although this must be balanced with the ever-present risk of hemorrhagic complications.

VA ECMO is utilized in a variety of shock circumstances. In cardiogenic shock, the use of VA ECMO has been associated with outcomes that are superior to historical values. VA ECMO has been reported as a mechanism of support in cardiogenic shock from various forms of cardiomyopathy, fulminant myocarditis, and obstructive shock from valvular disease or pulmonary emboli. In addition, many centers perform extracorporeal resuscitation (ECPR) in instances where conventional cardiopulmonary resuscitation and advanced cardiac life support measures have failed. There have been small clinical trials that demonstrate an immense potential benefit for ECPR, although these studies were conducted at single tertiary centers. This intervention certainly comes with high mortality and is quite resource and labor intensive. There are several ongoing studies examining VA ECMO in patients with cardiogenic shock in addition to studies examining ECPR specifically. As more and more centers embrace the use of this technology, there will be many opportunities for collaboration in developing a more robust understanding of the best practices associated with VA ECMO and the development of ECPR protocols where available.

Extracorporeal CO_2 Removal

In $ECCO_2R$, smaller cannulas are utilized to drain and return blood from the body, with a sole purpose of CO_2 elimination. This allows for a lower rate of vascular complications, a lesser need for anticoagulation, and better patient tolerance of the cannulas. Importantly, the lower blood flows generated through the cannulas in this circumstance are generally insufficient to provide more than a modest degree of support in oxygenation. The efficiency of carbon dioxide elimination, however, enables excellent control of hypercapnia, even with relatively low blood flow rates. There have been systematic reviews demonstrating that the majority of patients treated with $ECCO_2R$ for exacerbations of chronic obstructive pulmonary disease (COPD) were able to either avoid endotracheal intubation or weaned more quickly from mechanical ventilation after application of $ECCO_2R$. No randomized controlled trials have been done to evaluate the impact of $ECCO_2R$ on mortality in any context. However, some retrospective analyses demonstrated a clinically and statistically significant improvement in ICU and hospital lengths of stay associated with the use of $ECCO_2R$ in exacerbations of COPD. While the impact of this technology on outcomes in ARDS has yet to be established, multiple proof-of-concept studies have demonstrated the efficacy of $ECCO_2R$ in supporting CO_2 elimination in patients with ARDS and thus facilitating ultraprotective ventilation strategies. $ECCO_2R$ is not yet widely commercially available, and multiple clinical trials are attempting to define the role it may play in supporting critically ill patients with respiratory failure.

Patient Selection and Complications

ECLS should be considered in patients who have either respiratory, cardiac, or combined respiratory and cardiac failure that is advanced, life threatening, and refractory to less invasive measures of support. In keeping with the varying evidence described in the use of ECLS earlier, improving understanding of who most benefits from

this technology from a patient selection standpoint is paramount. ECLS is expensive, resource intensive, and fraught with complications (described Table 89.2). The database of the Extracorporeal Life Support Organization has been utilized to assess predictors of mortality on ECLS. These predictors can be analyzed using the survival after veno-arterial-ECMO (SAVE) and respiratory ECMO survival prediction (RESP) risk assessment tools, which have shown benefits in patient selection. For patients placed on VV ECMO, renal failure, advanced age, immunocompromised status, and associated nonpulmonary infection were among the variables associated with impaired hospital survival. Among those treated with VA ECMO, chronic renal failure, lower serum bicarbonate level, lower pulse pressure, and congenital heart disease were associated with increased mortality. Longer duration of pre-ECLS mechanical ventilation and prior cardiac arrest were associated with increased mortality on both modes of ECLS.

TABLE 89.2 ECMO Modes and Complications

ECMO Mode	Complications
VV ECMO	Bleeding (GI bleeding, intracranial hemorrhage) Cannula malposition or dislodgement Oxygenator failure Ventilator-associated lung injury from high airway pressures Bloodstream infection from cannula sites Recirculation Ischemic stroke Hemolysis
VA ECMO	Limb ischemia due to distal reperfusion issues in femoral cannulation Aortic insufficiency/regurgitation due to retrograde flow North-south syndrome Hemolysis Higher bleeding risk than in VV ECMO Air embolism

ECMO Mode	Complications
$ECCO_2$**R**	Inadequate oxygenation Ineffective CO_2 removal Acid-base imbalances

$ECCO_2R$, extracorporeal CO_2 removal; GI, gastrointestinal; VA ECMO, venoarterial extracorporeal membrane oxygenation; VV ECMO, venovenous extracorporeal membrane oxygenation.

In general, patients with acute, treatment-refractory cardiac or pulmonary disease should be considered for ECLS when they have good premorbid functional status and reasonable physiologic function outside their acute illness. ECLS in and of itself is not a curative therapy, and the reversibility of the underlying pathophysiology should be considered prior to initiation of ECLS. Consideration of ECLS should occur early in the course of disease and involve a collaborative team of physicians, surgeons, nurses, and respiratory therapists who are familiar with the technology. The RESP and SAVE scores provide a useful understanding of factors associated with a greater likelihood of survival on ECMO. However, the RESP score did not predict mortality with as much accuracy in patients with ARDS secondary to COVID-19. While these scoring tools do provide a framework for patient selection, a comprehensive decision involving risk and benefit analysis for each particular patient must be undertaken prior to initiating ECLS.

Complications specific to ECLS can involve mechanical issues related to the ECMO device, vascular damage from the cannulas, and complications associated with anticoagulation. The Extracorporeal Life Support Organization registry tabulates data regarding ECMO outcomes and complications. Pump failure is relatively uncommon; however, oxygenator failure is a known complication, particularly in patients with extended ECMO runs, as clot aggregation within the oxygenator increases over time. Bleeding is less common but still a very real concern as patients on ECMO who suffer gastrointestinal (GI) bleeding or, the most feared

complication, intracranial hemorrhage, historically have poor outcomes. Bleeding rates, as described earlier, tend to be increased in VA ECMO as those patients require higher degrees of anticoagulation. Infectious complications are similar to those seen in other settings involving central venous access, although there may be a slight increase in the incidence of fungemia among patients on ECLS. Long-term outcomes after ECLS, including potential functional and psychological outcomes, are poorly understood and represent an area of active research. Post-ICU clinics, and specifically post-ECMO clinics, are being actively implemented, and the data collected from them will ideally allow for the delivery of proactive ICU care.

Management of Patients on Extracorporeal Life Support

The comprehensive management of patients on ECLS is complex and should be undertaken by clinicians with experience in dealing with this particular patient population. The optimal mode of mechanical ventilation on ECLS is controversial. Some centers engage in a practice of “lung rest,” in which patients are placed on minimal vent settings and may even be removed from the ventilator entirely. Others provide aggressive lung recruitment with higher pressures to attempt to encourage improved pulmonary functionality. Whatever mode of ventilation is selected should represent the clinician’s best effort at preventing any further lung injury while ECLS is continued. ECLS does not represent a curative intervention aimed at treating the underlying disease. An important principle, therefore, is to avoid exacerbating organ injury while providing support.

Anticoagulation remains a complex problem in ECLS. It is difficult to balance preventing thrombosis in the ECLS circuit while avoiding bleeding complications in the patient. A wide array of tests can be used to monitor levels of anticoagulation. Decisions about which to use should be made in the context of the specific center treating the

patient with awareness of their particular laboratory's strengths and weaknesses.

Some patients are stable enough to ambulate on ECLS. Physical therapy is an important part of ICU care for all critically ill patients, and patients receiving ECLS are at high risk for developing critical care myopathy as they often have extended ICU hospitalizations. Many centers employ ambulation programs or bedside physical therapy to try and maintain strength and stamina while patients are on ECLS. Analgesia should be provided as needed, but sedation should be limited to whatever is necessary to ensure safety and comfort without preventing rehabilitation, whether it includes ambulation.

Separating From Extracorporeal Life Support

Patients are supported with the appropriate mode of ECLS for the duration of the time needed to support recovery. In some cases, organ recovery is not achieved despite aggressive measures to treat the underlying cause of dysfunction. Those represent ethically challenging cases, as patients may be awake and appear stable on full support with no viable exit strategy. In those instances, open and honest discussions regarding the propriety of continued support should involve patients and families, with the aim of reaching the decision most consistent with their goals. In patients who do recover, ECLS can be weaned by way of decreasing blood flow rate through the oxygenator, the FDO_2, and the sweep speed until organ recovery is sufficiently achieved to allow for adequate functionality on appropriate levels of ventilatory and hemodynamic support. At that point, the cannulas can be removed, and usual critical care can continue to be provided.

SUGGESTED READINGS

Barbaro RP, MacLaren G, Boonstra PS, et al; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet*. 2021;398(10307):1230-1238.

Retrospective analysis utilizing ELSO data on 4,812 patients with COVID ARDS at 349 centers in 41 countries who were treated with ECMO. Overall mortality increased throughout the pandemic as did the average length of ECMO run.

Braune S, Sieweke A, Brettner F, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med*. 2016;42(9):1437-1444.

Case-control study of 50 patients at five European centers comparing $ECCO_2R$ versus traditional critical care comparing intubation rates and mortality. $ECCO_2R$ patients had lower intubation rates but more complications from ECLS. No difference in mortality was found.

Cho SM, Canner J, Caturegli G, et al. Risk factors of ischemic and hemorrhagic strokes during venovenous extracorporeal membrane oxygenation: analysis of data from the Extracorporeal Life Support Organization Registry. *Crit Care Med*. 2021;49(1):91-101.

Retrospective analysis of ELSO data on 15,872 patients who were treated with VV-ECMO found that 5.1% suffer strokes (3.1% hemorrhagic and 1.4% ischemic) and this markedly increases mortality. Notably multiple pre-cannulation factors were noted to increase stroke risk.

Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-1975.

Randomized control trial (EOLIA trial) on 249 patients with severe ARDS comparing VV-ECMO with conventional management. Found no mortality benefit although there was significant crossover (28%) of patients from the conventional arm who were eventually cannulated for VV-ECMO. Multiple secondary endpoints indicated benefit to ECMO.

Joshi H, Flanagan M, Subramanian R, Drouin M. Respiratory ECMO survival prediction (RESP) score for COVID-19 patients treated with ECMO. *ASAIO J*. 2022;68(4):486-491.

Retrospective analysis of 1,985 patients with COVID ARDS treated with VV-ECMO looking at predictive value of the RESP score. The RESP score was found to be less predictive of mortality in COVID patients when compared with the previous RESP score studies.

90 Basic Critical Care Ultrasound

Brandt Lydon and Adam Anderson

Introduction

Critical care ultrasound refers to clinician-performed and interpreted bedside ultrasound to help diagnose and manage patients who are critically ill with cardiopulmonary failure. Comparable to the physical examination, it is a noninvasive, rapid, and repeatable examination performed by the provider directly caring for the patient and is designed to answer specific clinical questions. The results are immediately available to guide time-sensitive decision-making. Multiple focused examinations are performed serially to document clinical responses to specific interventions. It differs from standard echocardiography and ultrasonography, which provide delayed, comprehensive, and mostly single examinations for diagnostic purposes. These examinations are interpreted by physicians who are disassociated from the clinical care of the patient.

Ultrasound is an ideal modality for bedside use in the intensive care unit (ICU) and should be used for both diagnostic purposes and procedural guidance. Ultrasound involves no ionizing radiation, avoids patient transportation, and is repeatable. It functions as an extension of the physical examination. Barriers to the use of ultrasound in patients who are critically ill include inadequate training, the cost of equipment, difficulty in achieving adequate ultrasound windows in patients who are ill for various reasons (obesity, dressings, incisions), and the risk of transmitting infections if a cleaning protocol for the probes and device is not followed.

Appropriate clinical application of the technology is dependent on the knowledge and skill of the operator/interpreter. Expertise in critical care ultrasound requires a combination of didactic training, as well as many hours of bedside scanning and image interpretation sessions to review common pathologies. Critical care ultrasound is best learned at the bedside from a mentor who is an expert in the field. Societal guidelines have been published, defining minimum criteria for achieving initial competence in critical care and focused cardiac ultrasonography. The reader is encouraged to review these documents in the “Suggested Readings.”

This chapter is a *brief* introduction to basic critical care diagnostic ultrasound. Topics include lung, cardiac, and abdominal ultrasound, as well as their application in the evaluation of patients with acute respiratory failure and shock (Table 90.1).

TABLE 90.1 Comparison of Bedside Ultrasonography With Common Diagnostic Modalities Used in the Intensive Care Unit

Modes of Assessment	Immediately Available	Easily Repeatable	Specific/Sensitive	Noninvasive/Safe	Interpreted by Bedside Provider
History and physical	Yes	Yes	+/−	Yes	Yes
Chest x-ray	No	No	+/−	+/−	+/−
Chest CT scan	No	No	Yes	+/−	+/−
NICOM	Yes	Yes	+/−	Yes	Yes
Pulmonary artery catheter	No	Yes	+/−	+/−	Yes
Formal echo	No	No	Yes	Yes	+/−
Bedside ultrasound	Yes	Yes	+/−	Yes	Yes

CT, computed tomography; NICOM, noninvasive cardiac output monitoring.

BASIC ULTRASOUND PHYSICS

Ultrasound refers to sound waves with a frequency more than 20 kHz, which is too high for the human ear to hear. These high-frequency waves are used to generate images of internal organs and can also detect blood flow velocities. Sound waves (vibrations) are transmitted through different media (solid, liquid, or gas) and are governed by the following relationship: propagation velocity = frequency × wavelength. In body tissues, sound waves propagate at approximately 1,500 m/s. Therefore, if the frequency of the waves is 1,000 Hz (cycles per second), the wavelength is 1.5 m, which is obviously inadequate for human ultrasound imaging since many of the tissues of interest are only millimeters thick.

Therefore, extremely high-frequency sound waves are used in medical ultrasound (in the range of 2-15 MHz). Ultrasound waves with higher frequency will deliver higher-resolution images, but this needs to be balanced with the ability of the ultrasound waves to penetrate into the body. Lower-frequency ultrasound waves tend to be less attenuated by tissue and penetrate further.

Ultrasound waves have been historically generated by a piezoelectric crystal transducer within an ultrasound probe. Electrical energy is converted by the crystals into movement and vibrations, which set up the ultrasound waves that propagate into the surroundings. The unique properties of each crystal will determine the frequency of the waves generated. The transducer probes not only generate the sound waves but also receive returning waves from the tissues. Pulses of sound waves are generated by the transducer and then received back. It is this pulsed natured of the signal and

the time delay between generation and reception which allow for the ultrasound machine to derive the distance of the structure of interest from the probe. Thousands of pulses per second are possible with modern machines. The returning waves are converted back to an electrical signal, which is then amplified and processed to generate the final image. This image provides information about the depth and tissue characteristics of the structures encountered by the sound waves. Modern transducer probes often have these crystals arranged in electronically steered or phased arrays, to generate a complete image from multiple wavelets that are generated in a series of radial lines. New technologies have emerged that use 2D (two-dimensional) silicon chips to generate ultrasonic waves, allowing a single handheld device to perform the tasks of multiple different probe configurations.

The echogenicity of a particular tissue is determined by the degree of reflection of the ultrasound waves at tissue interfaces. If most of the waves are reflected back at a tissue interface, the tissue will appear very bright or hyperechoic. An example of this is bone, which reflects most ultrasound waves and will not allow for visualization of the structures deeper to the bone. If most of the waves penetrate through the interface without reflection of the waves, the tissue will appear darker or black (hypoechoic). This is typically seen with fluids. Varying degrees of gray are therefore seen with tissue imaging, dependent on the properties of the tissue.

ULTRASOUND MACHINE

Modes

- **2D or B-mode** (brightness mode): standard, familiar default mode that generates slice images. The machine processes the returning sound waves and displays structures as a grayscale cross-sectional image.
- **M-mode** (motion mode): plots motion over time. This mode provides excellent temporal resolution and is useful for visualizing moving structures and measuring cavity dimensions.
- **Doppler:** The Doppler effect refers to a frequency change that occurs in the echo signal when an object moves toward or away from the source of the ultrasound waves. If a wave source is moving toward an observer, the waves are compressed, causing a decrease in the wavelength. The opposite applies if the wave source is moving away from the observer.
  - **Continuous wave (CW) Doppler** uses a continuous cycle of ultrasound waves with simultaneous acquisition of the returning echoes. The ultrasound machine analyzes the complex mix of returning echoes and Doppler shifts and generates a spectral Doppler layout from which it is able to discern the direction of flow, as well as the peak velocity and mean velocity. CW Doppler is used routinely to measure high-velocity flows in the heart across valves. It is also useful for estimating pulmonary artery systolic pressures.
  - **Pulse wave (PW) Doppler** allows for depth discrimination to determine where a particular Doppler shift signal arises along the ultrasound beam axis (the sample

volume). PW Doppler is used in assessing blood velocity at a specific location of interest and is best used with low-velocity flows, as it is susceptible to a phenomenon called aliasing (Nyquist limit). PW Doppler is commonly used to assess the velocity of blood in the aortic outflow tract to estimate stroke volume.
    - **Color Doppler** is a form of pulsed-wave Doppler using a grid with multiple interrogation points (pixels) and is generally superimposed on the 2D image to determine direction and velocity of flow in a large sample area.
- **Limitations of Doppler:** The major limitation of Doppler is the need to align the ultrasound beam with the direction of the blood flow (the "angle of insonation"). This angle should at a maximum be 15° to ensure accuracy.

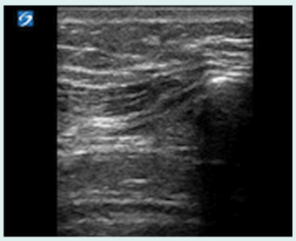
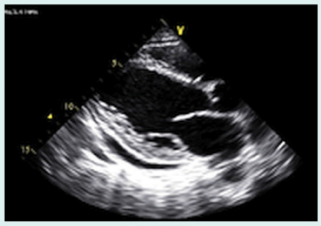
Adjustable Settings

- **Gain:** Adjustments in gain allow the operator to change the brightness of the image and should be set to allow the maximum contrast resolution for the area of interest. Many machines have total gain, near-gain, and far-gain settings, and users should try to set uniform gain across the image.
- **Depth:** The depth should be adjusted so that the area of interest is viewed in the middle of the ultrasound screen. Appropriate depth settings can often improve resolution.

Transducers

- Transducers vary by frequency and footprint (Table 90.2).
- **Frequency:** number of cycles of compressions and rarefactions that occur in 1 second and is inversely proportional to wavelength
    - Higher-frequency transducers generate higher-resolution images but do not penetrate deeply into tissues. These are typically used to visualize superficial structures like vessels and nerves and are used for procedures like central line insertion. Most linear vascular probes have a frequency of 5 to 10 MHz.
    - Lower-frequency transducers (1.0-5.0 MHz) are commonly used as phased-array probes for cardiac, lung, and abdominal imaging, as they provide more penetration to visualize deeper structures.
- **Footprint:** size and shape of probe area in contact with skin

TABLE 90.2 Characteristics, Uses, and Advantages of Three Commonly Used Transducers

	Linear	Phased Array	Curvilinear
Footprint			
			
Frequency	5-10 MHz	1-5 MHz	2-5 MHz
Depth	9 cm	35 cm	30 cm
Uses	Vascular, lung, superficial structures	Cardiac, abdominal, lung, pleura, IVC	Abdominal, FAST exam
Advantages	Higher resolution	Small footprint fits between rib spaces	Large footprint with wide field of view

FAST, focused assessment with sonography for trauma; IVC, inferior vena cava.

Standard Transducer Movements

- **Slide/move:** movement of ultrasound footprint across skin surface (eg, sliding probe vertically down anterior chest to evaluate lung slide between different rib spaces)
- **Rotate:** turning clockwise or counterclockwise without angling or changing the location on the body, in order to obtain an orthogonal plane (eg, moving from a parasternal long axis [PLAX] to a parasternal short axis [PSAX])
- **Fan/tilt:** angling the probe perpendicular to its long axis in the same location (eg, angling side-to-side in the subcostal view to appreciate the aorta running laterally to the vena cava)
- **Rocking:** angling the probe parallel to its long axis in the same plane and location (eg, angling the probe to shift focus from the left ventricle to the right ventricle while maintaining an apical four-chamber view)

Lung Ultrasound and the Evaluation of Acute Respiratory Failure

KEY POINTS

- Air has classically been considered the enemy of ultrasound, as its reflective properties inhibit the ultrasound signal from reaching underlying structures.

- Lung ultrasound is therefore generally restricted to patterns seen at the pleural surface.
- More than 90% of etiologies of acute respiratory failure involve the pleural surface and cause ultrasound artifacts.
- These artifacts create specific patterns that correlate to traditional physical examination findings. These artifacts or lung ultrasound signatures, define lung ultrasound. They include lung slide, A-lines, B-lines, consolidation, and effusion.
- Lung ultrasound is superior compared to chest x-ray and comparable to computed tomography (CT) in the detection of pneumothorax, normal aeration patterns, interstitial syndrome, consolidation, and pleural effusion.
- The Bedside Lung Ultrasound in Emergency (BLUE) protocol is a rapid noninvasive examination that provides a decision tree framework to help delineate the most likely etiology in patients with acute respiratory failure (Figure 90.1).

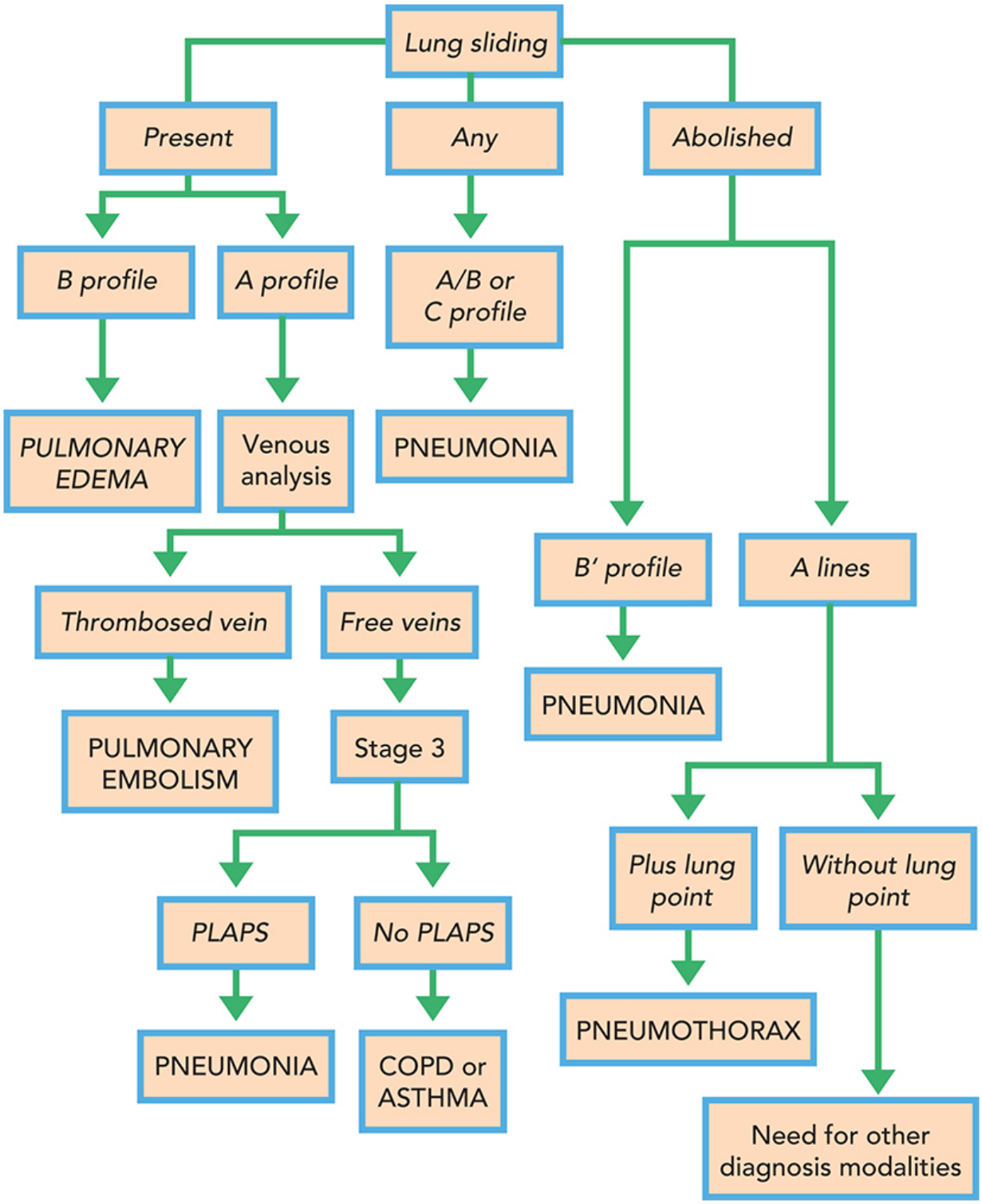


FIGURE 90.1 **A decision tree using lung ultrasonography to guide diagnosis of severe dyspnea**. COPD, chronic obstructive pulmonary disease; PLAPS, posterolateral alveolar and/or pleural syndrome.

PERFORMING THE EXAMINATION

Probe Selection (Figure 90.2)

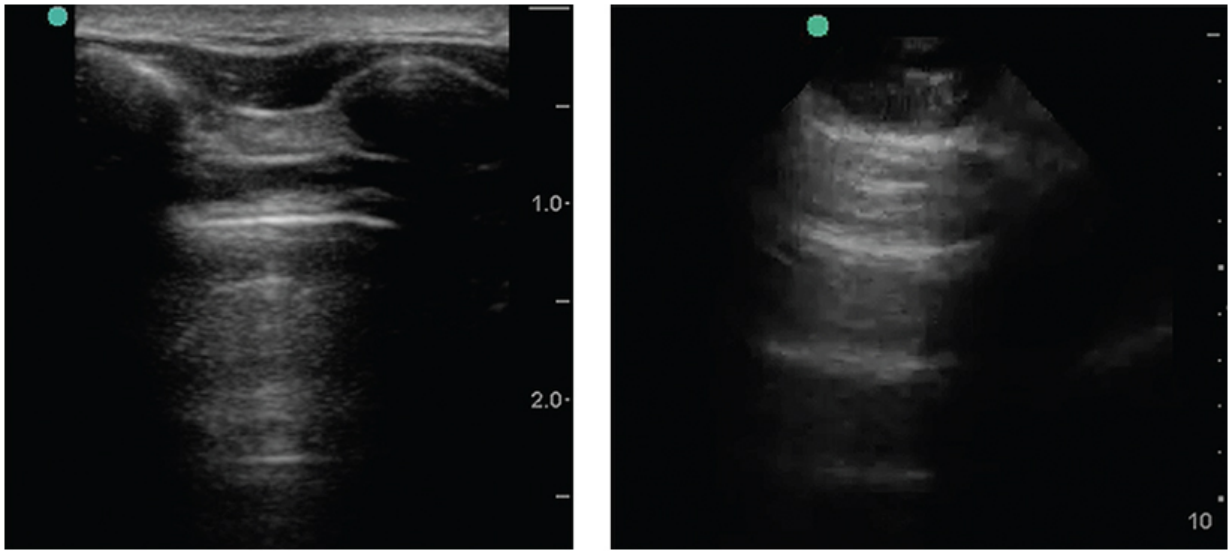


FIGURE 90.2 Comparison of normal lung ultrasound using a linear probe (**left**) and a phased-array probe (**right**). Notice the higher resolution with the linear probe; however, it can only penetrate a few centimeters.

- **Phased-array probe**
  - Set the depth to 15 cm to evaluate for consolidation, pleural effusions, and to identify the diaphragm.
  - Able to appreciate lung slide; however, it provides less resolution of the pleural surface compared to linear probes. Decreasing the gain setting will make the pleural line more apparent.
  - Has the advantage of not needing to switch transducers to perform a rapid and sequential lung, cardiac, and abdominal examination in a deteriorating patient.
- **High-frequency, linear probe**
  - Has better resolution of superficial structures, making it easier to evaluate the pleural interface, including detecting lung slide and lung point.
- **Micro-convex probe**
  - Small footprint allows for easy visualization between rib spaces.
  - Frequencies between 5 and 8 MHz.

Machine Settings

- **Basic/abdominal setting:** Avoid machine's advanced settings (ie, cardiac presets), which diminish the artifacts that define lung ultrasound.

Probe Positioning (Figure 90.3)

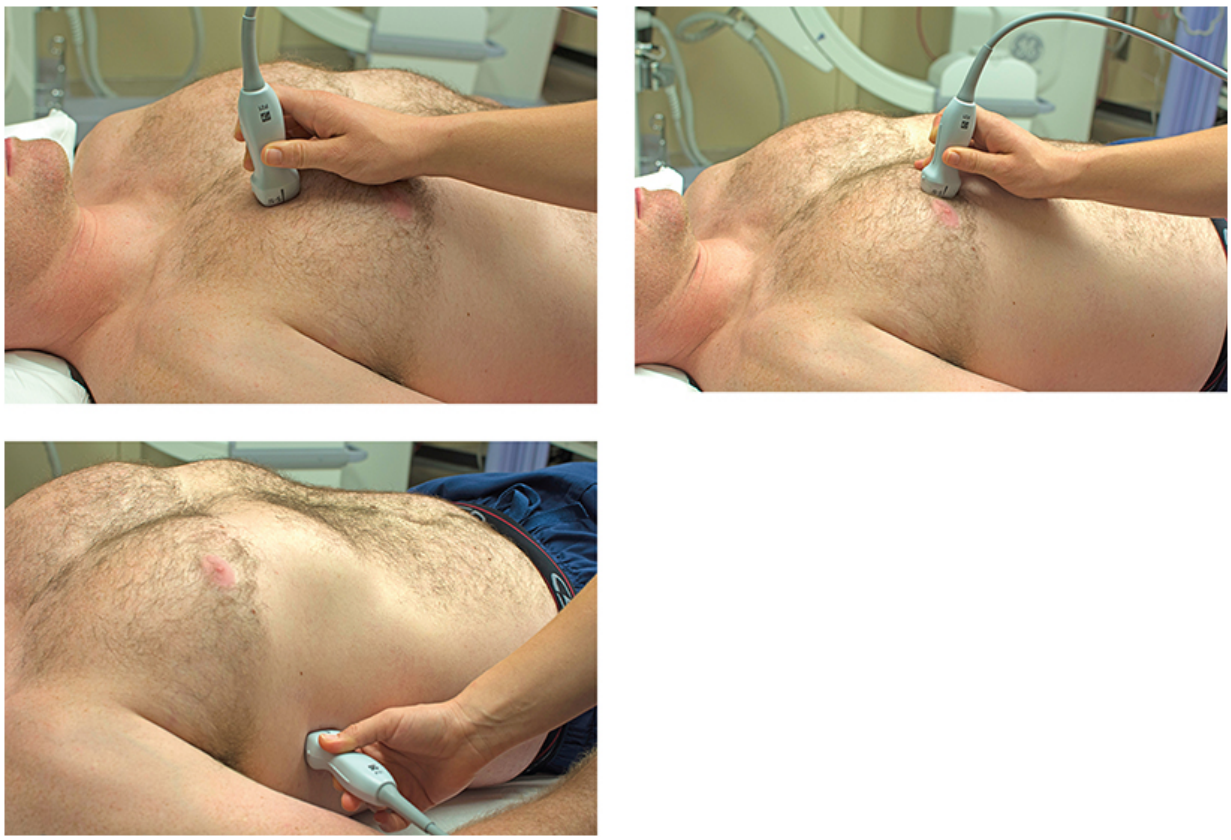


FIGURE 90.3 **To evaluate for A-lines, B-lines, and lung slide, place the transducer on the anterior chest perpendicular to the chest wall and slide between the rib spaces with the indicator at 12 o'clock**. To evaluate for pleural effusions, atelectasis/consolidation, and subdiaphragmatic structures, place the transducer in the mid-axillary line with the indicator at 12 o'clock. Slide the transducer superiorly and inferiorly until the diaphragm is identified. To completely evaluate this area, it may be necessary to move the transducer more posteriorly while angling upward toward the horizon.

- **Sagittal/longitudinal**, indicator pointing to 12 o’clock, **perpendicular** to chest wall.
- *Bilateral anterior chest*: Examine artifacts between multiple rib spaces over the anterior chest, starting apically and moving caudad.
  - Convention is to include both adjacent rib shadows on the image to assess the underlying pleura and lung.
  - Multiple parallel and vertical scan lines are recommended.
- *Bilateral posterior and lateral axillary position* (*PLAPS [posterolateral alveolar and/or pleural syndrome] point*): Obtain images in the mid-axillary and posterior axillary lines, identify the diaphragm, evaluate for consolidation and pleural fluid, and assess subdiaphragmatic structures (liver/spleen). To do this correctly, the operator often needs to start very posteriorly and angle the probe toward the horizon.

THE FIVE LUNG SIGNATURES

1. Lung Slide

Characteristics

- Horizontal hyperechoic line approximately 0.5 cm deep to the origin of rib shadows
- Dynamic finding, variably described as having a shimmering, sparkling, glimmering, twinkling appearance
- Represents the movement of the visceral pleura on the parietal pleura. Is often more apparent at the lung base than at the apex of the lung
- Presence of lung slide rules out pneumothorax at the point of interrogation.
- Lung pulse is not the same as lung slide but refers to pulsation of the pleural line interface with each cardiac pulsation. Its presence excludes a pneumothorax.
- Using M-mode, normal lung slide results in a finding described as the "sandy beach sign." This provides evidence of movement of the underlying lung, underneath the pleural line (the sand on a beach), as opposed to the relatively stationary superficial soft tissue structures (seen as "waves" on M-mode imaging). If a pneumothorax is present, the M-mode finding is referred to as the stratosphere sign or barcode sign and consists of multiple horizontal lines on the screen without the haziness generated by lung motion (Figure 90.4).
- Lung POINT: sign referring to the point or edge of a pneumothorax. Sliding lung is seen coming in and out of the ultrasound image as the patient breaths and is juxtaposed to an area with absent lung slide. This finding is specific for pneumothorax but not very sensitive, as it is not always seen and depends on pneumothorax location related to probe position.

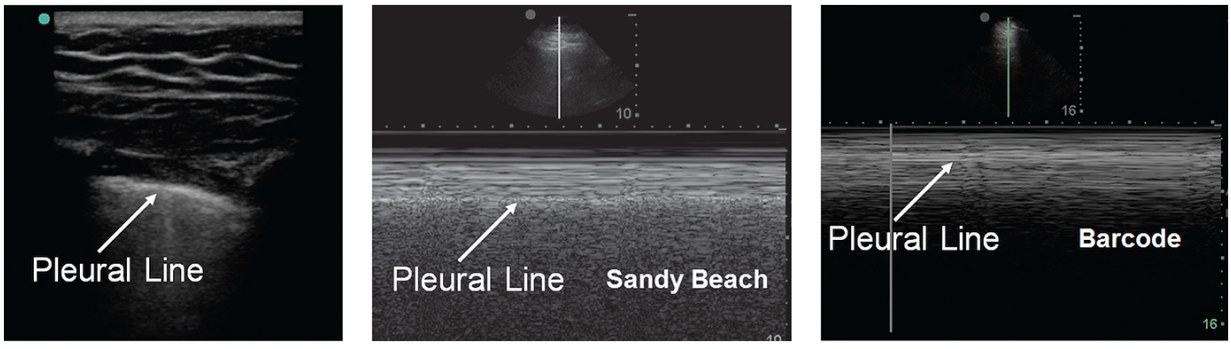


FIGURE 90.4 Lung slide represents the movement between the visceral and parietal pleura and is displayed as a bright, shimmering line between rib shadows (**left**). Movement beneath the pleural line can be assessed using M-mode. If the lung is in contact and moving below the pleural line, a grainy or sandy pattern is seen (**middle**). If there is no movement or the lung is not in direct contact with the parietal pleura, then a linear pattern is represented (**right**). These patterns are referred to as the sandy beach and stratosphere/barcode signs, respectively.

Differential Diagnosis for Loss of Lung Slide

- Pneumothorax
- Severe pneumonia or acute respiratory distress syndrome (ARDS) with significant loss of lung compliance
- Prolonged apnea
- History of pleurodesis
- Examination on the left side with right mainstem intubation
- Bullous lung disease
- Adhesions
- Pulmonary contusions

2. A-Lines

Characteristics

- A-lines are a reverberation artifact resulting in serial repetitions of the pleural line.
- A-lines are horizontal lines and are each separated by an equal distance (this is a reverberation artifact of the original distance from the probe to the pleural line).
- A-lines are the result of air at the pleural interface, whether from normal aerated lung or pneumothorax.

Differential Diagnosis

- Normal lung, chronic obstructive pulmonary disease (COPD)/asthma, pneumothorax (A-lines with absent lung slide), pulmonary embolism (without a pulmonary infarct)

3. B-Lines

Characteristics

- Vertical, hyperechoic, dominant lines
- Originate at the pleural surface and extend to the bottom of the screen without fading
- Efface A-lines where the two intersect
- Move in synchrony with lung slide
- Their presence excludes pneumothorax.
- Represents thickened subpleural interlobular septae surrounded by air-filled alveoli
- The more B-lines and the closer they are together signifies a more severe involvement of the interlobular septae and progressive alveolar involvement

Differential Diagnosis

- ARDS, cardiogenic pulmonary edema, pneumonia, lung contusion, interstitial lung disease
- Multiple anterior and symmetric B-lines generally signifies cardiogenic pulmonary edema.
- Asymmetric B-lines interspersed with normal areas of A-lines suggests noncardiogenic edema/ARDS, pneumonia (Figure 90.5).

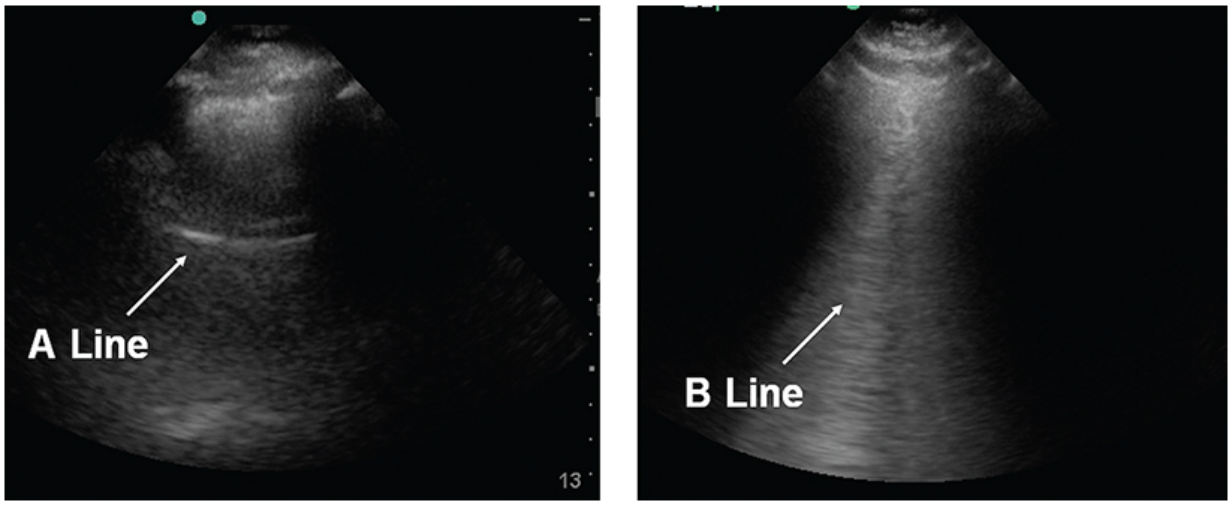


FIGURE 90.5 A-lines, created by reflections of the pleural line, are equidistant horizontal lines (**left**). B-lines are dominant, bright vertical lines that move with the pleura, extend to the bottom of the screen, and represent thickened, fluid-filled interlobular septae (**right**).

4. Consolidation

Characteristics

- The lung is no longer air-filled and so no A- or B-lines are seen. The consolidated or atelectatic lung appears like any other solid organ (“hepatization” of the lung).
- Best seen in lateral views just above the diaphragm
- Often associated with effusions
- Air bronchograms may be seen in the consolidated lung:
  - Dynamic air bronchograms appear as hyperechoic artifacts that slide with respiration and represents the movement of air within bronchi of the consolidated lung, suggesting preserved patency of the proximal airway.
  - Static air bronchograms appear as a hyperechoic artifact that does not move throughout the respiratory cycle.
  - Dynamic air bronchograms suggest a pneumonic consolidation, while static air bronchograms cannot reliably differentiate a pneumonia from atelectasis.

Differential Diagnosis

- Atelectasis, pneumonia, ARDS, tumor or mass, lung contusion

5. Pleural Effusion

Characteristics

- Pleural fluid is hypoechoic or anechoic (black) on ultrasound.
- Most effusions are free-flowing, though complex or loculated effusions may not be dependent. The patient should be positioned to optimize the view and the entire hemithorax interrogated.
- Ultrasound can detect very small pleural effusions before they are seen on a chest x-ray (CXR).
- There should be at least 1 cm of pleural fluid before an attempt at thoracentesis is performed.
- Ultrasound of pleural fluid reveals it to be dynamic, meaning there is movement with respiration.
- It is always important to define the boundaries of the pleural fluid:
  - The boundaries of the pleural space consist of the chest wall, the diaphragm, and the lung.
  - This is a routine but extremely important component of pleural ultrasound, to avoid misidentifying the diaphragm and confusing it with the perirenal fascia.
  - Accurate identification of the diaphragm helps to avoid subdiaphragmatic injury during pleural procedures.
- Fluid characteristics:
  - Simple fluid is anechoic.
  - Exudates may not be anechoic and may have what appears to be swirling debris within the fluid (plankton sign).
  - Complex effusions may have multiple fibrous strands and septations within the effusion that are often not seen with CT.
    - This may signify loculation of the fluid and could be due to a parapneumonic effusion, empyema, or a resolving hemothorax (Figure 90.6).

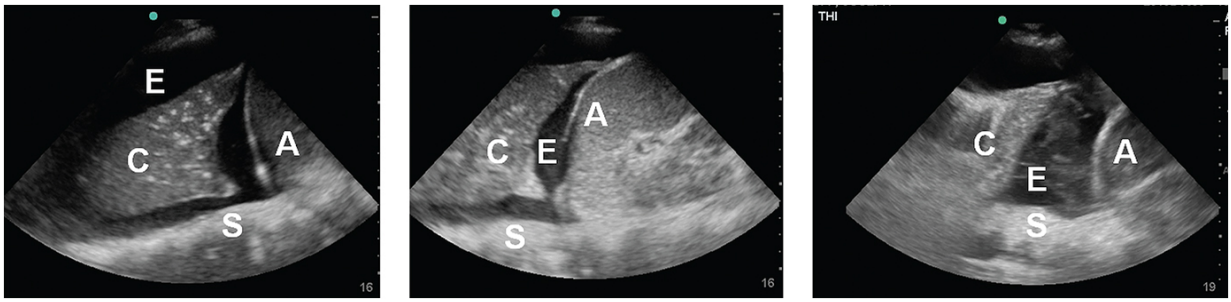


FIGURE 90.6 **Three examples of lung consolidation and effusions**. A consolidated lung has a similar echogenicity to the abdominal organs. Effusions are anechoic or black. Notice the echogenic material in the pleural fluid in the image on the right. This can be seen

in complex effusions and suggests the need for a chest tube. The diaphragm is visualized as a hyperechoic line above the abdominal structures. The spine can be seen posteriorly. A, abdominal structures; C, consolidation; E, effusion; S, spine.

APPROACH TO ACUTE RESPIRATORY FAILURE

An algorithmic approach using a combination of lung ultrasound, coupled with a lower extremity venous examination, is recommended when using ultrasound to help determine an etiology for acute respiratory failure. In clinical practice, the history, examination findings, laboratory data, and basic imaging are combined with the knowledge of the bedside ultrasound examination to help determine what the most likely etiology for respiratory failure is. This algorithm is known as the BLUE protocol (Figure 90.1) and is reviewed conceptually later by a simple approach to bedside lung ultrasound.

- Is there a pneumothorax? Is lung slide present?
  - If NO lung slide, pneumothorax is possible. Is there lung point present to confirm a pneumothorax? Are B-lines or lung pulse present, which will rule out a pneumothorax at the probe position?
  - Consider other causes of loss of lung slide, as noted earlier.
- Are the lungs normally aerated (dry), as signified by an A-line predominant pattern?
  - If yes, there is unlikely to be a parenchymal disease but rather an airways (COPD/asthma), vascular (pulmonary embolism [PE]), or pleural process.
- Is there an interstitial or alveolar process (wet) as signified by B-lines?
  - Are the B-lines diffuse, bilateral, and symmetric?
    - Suggestive of cardiogenic pulmonary edema
  - Are the B-lines occasional, asymmetric, and interspersed with normal areas of A-lines?
    - Suggestive of noncardiogenic edema or pneumonia
- Is there an asymmetric A/B profile (one lung has A pattern, the other has B pattern)?
  - Suggestive of pneumonia, which may be confirmed by the finding of consolidation and dynamic air bronchograms
- Is there a pleural effusion present, and does it appear to be simple or complex? Is it safe to proceed with thoracentesis?

Focused Echocardiography

KEY POINTS

- Bedside echocardiography is goal-directed and problem-oriented.
  - Why is the patient hypotensive? What is the cause of hemodynamic instability?

    - Is there a pericardial effusion? Is there tamponade physiology?
    - Is the left ventricular (LV) function normal, hyperdynamic, moderately, or severely depressed?
    - What is the right ventricular (RV) size and function? Are there signs of RV strain?
    - Are there any gross valvular or wall motion abnormalities?
    - Is the inferior vena cava (IVC) normal, distended, or collapsible?
    - Can more fluid be tolerated?
- A phased-array probe is used with the machine on cardiac setting (indicator on right side of screen).
- Five standard views are obtained while the patient is in a supine position.
- Focused critical care echocardiography complements standard comprehensive echocardiography but does not replace it.
- Critical care echocardiography **should be viewed as an extension of the physical examination. Ultrasound findings should support clinical suspicion and help narrow differential diagnosis.**

LIMITATIONS

- Limited quantitative measurements and poorer image quality with portable bedside machines compared to comprehensive echocardiography
- Some significant findings are difficult to appreciate, including subtle wall motion abnormalities, valvular vegetations, and RV hypertrophy.
- Obtaining more than two cardiac views may not be possible due to patient body habitus, COPD/lung disease, bandages, and positioning in patients who are critically ill.
- Misinterpretation of findings occurs when the image is foreshortened or off-axis, when fewer than two views are obtained, or when image quality is poor, *and* the interpreter is not conscious of these examination limitations.
- Advanced diagnostic measurements (eg, M-mode and Doppler measurements) are particularly susceptible to off-axis or nonconventional images and should be interpreted with caution.
- Referral for standard, comprehensive echocardiography should be considered in situations where findings are inconclusive or fall beyond the scope of the point-of-care examination.

IMAGE ACQUISITION AND INTERPRETATION

Image window: position on patient's chest (parasternal, apical, and subcostal) (Figure 90.7)

A
B
C
D

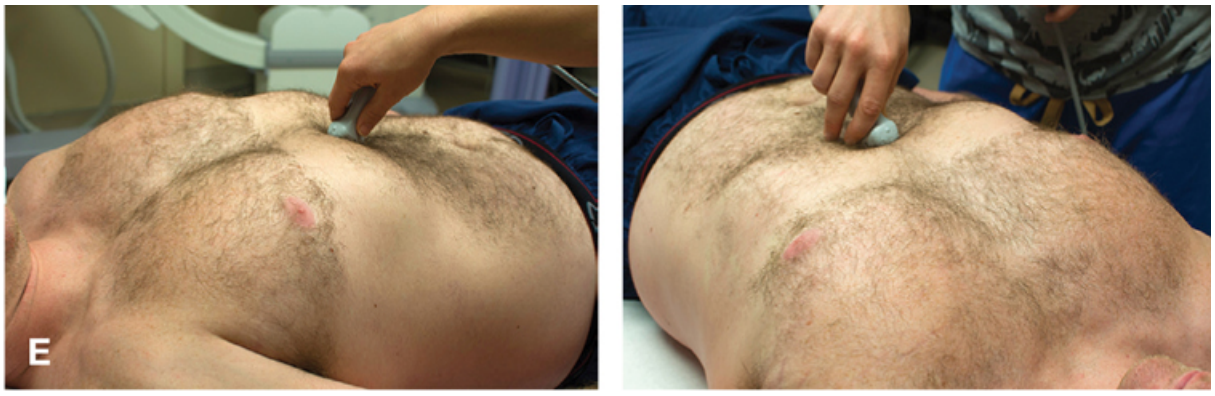


FIGURE 90.7 **Cardiac examination probe positions**. **A:** Parasternal long axis. **B:** Parasternal short axis. **C:** Apical long axis. **D:** Subcostal long axis. **E:** Subcostal IVC. IVC, inferior vena cava.

Image plane: three standard image planes defined by the American Society of Echocardiography—long axis, short axis, and four-chamber

- Long axis (sagittal plane): vertical bisection through LV apex and center of aortic valve
- Short axis (transverse plane): perpendicular to long axis, cross sections of ventricles
- Four-chamber (coronal plane): LV apex to base, bisecting mitral and tricuspid valves

1. PLAX

Image Acquisition

- Indicator toward patient's right shoulder (11 o'clock)
- Probe just left of sternum (between 2nd and 5th rib space)

Image Optimization

- Slide up and down along the left aspect of the sternum to locate the best viewing window.
- Stay close to the sternum to avoid lung interference.
- Find the interspace in which the inferior aspect of the septum is horizontal.
- Rotate so that mitral and aortic valves are in the same plane. May also need to tilt/fan slightly to achieve this.
- The left ventricle should be seen in its longest axis, and the aortic valve cusps should be symmetric.
- Rock away from sternum so that the mitral and aortic valves are in the center of the screen.

- The apex should not be visualized.
- Adjust depth so descending aorta is in view (14-16 cm) (Figure 90.8).

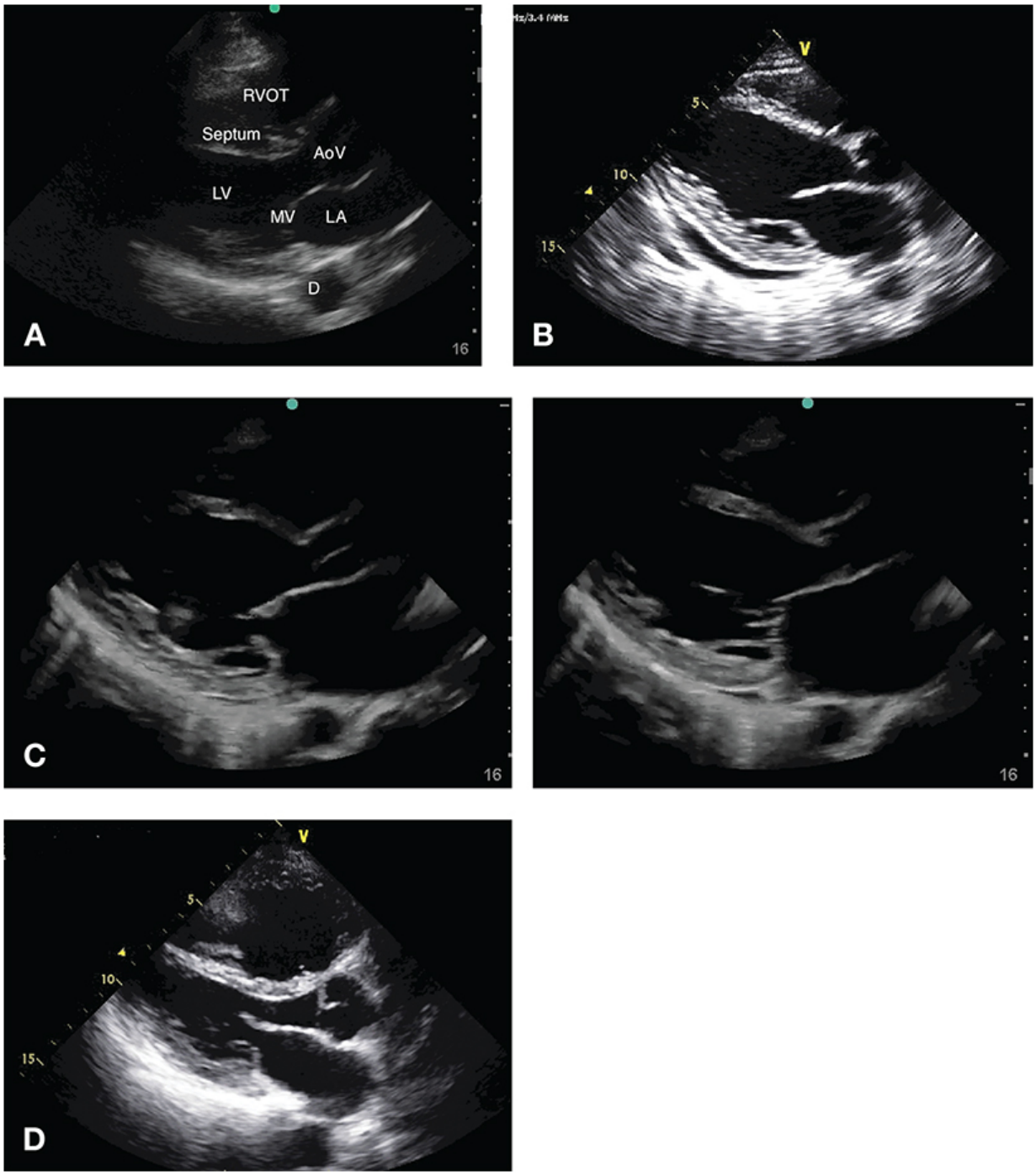


FIGURE 90.8 **A:** Normal PLAX. AoV, aortic valve; D, descending aorta; LA, left atrium; LV, left ventricle; MV, mitral valve; PLAX, parasternal long axis; RVOT, right ventricular outflow tract. **B:** Circumferential pericardial effusion. The posterior aspect lies between the posterior wall of the left ventricle and pericardium. Notice that pericardial fluid is superior to the descending aorta. **C:** Severe left ventricular dysfunction in diastole (**left**) and systole (**right**). Notice how the anterior leaflet of the mitral valve barely

opens and does not approximate the septum. The cavity is dilated and the walls hardly move inward during contraction. **D:** Right ventricular overload causing septal deviation toward the left ventricle.

Normal Structure and Function

- RV outflow tract, aortic outflow tract, and left atrium approximately the same size
- LV systolic function: Visualize myocardial thickening, symmetrical inward endocardial movement, anterior leaflet of mitral valve (MV) approximates the septum (<1 cm).
- Mitral and aortic valves: Leaflets come together with normal opening and closing.

Is There a Pericardial Effusion?

- Appears as anechoic space between the myocardium and pericardium
- Nonloculated effusions generally collect posteriorly in dependent areas.
- Anterior fat pad can be misinterpreted as an anterior effusion, since it is located between myocardium and pericardium.
- Ascites and left-sided pleural effusions can be mistaken for pericardial effusions.
- Use the descending aorta to differentiate between pericardial and pleural effusions. Pericardial effusions taper anterior to the descending aorta, pleural effusions extend posterior to the descending aorta.

Is There LV Dysfunction?

- Dilated chamber, decreased myocardial thickening
- Diminished MV opening, anterior leaflet more than 1 cm from septum

Is the LV Hyperdynamic?

- Small chamber size with anterior MV leaflet contacting the septum
- End systolic cavity obliteration

Is the Right Ventricle Overloaded?

- RV outflow tract larger than the aorta and left atrium
- Paradoxical septal motion

Pitfalls of Parasternal Long Axis

- Only visualizing RV outflow tract. Unless RV severely abnormal, unable to evaluate RV size
- May overestimate LV function in underresuscitated patients with sepsis or hypovolemia
- Off-axis views lead to underestimation of LV size and overestimation of function.

- Inaccurate assessment of MV or atrioventricular (AV) function:
  - Normal-appearing valves may have significant regurgitation (use color Doppler to better clarify).
  - Vegetations may be subtle and can be missed.
  - Heavily calcified-appearing AV may not be hemodynamically significant.

2. PSAX

Image Acquisition

- From a good PLAX view, rotate the probe clockwise 60° to 90°, until the left ventricle is circular.

Image Optimization

- Center the left ventricle in the screen between the rib shadows.
- Find the mid-ventricular level by tilting the probe along the right shoulder–left hip axis until the papillary muscles are visualized (they will come into view just below the MV, which looks like a fishmouth).
- Papillary muscles at 4 and 7 o'clock positions

Normal Structure and Function

- Circular LV with small, crescent-shaped RV
- LV systolic function: Endocardium moves symmetrically toward center, equal ventricular thickening, papillary muscles approximate during end systole (Figure 90.9).

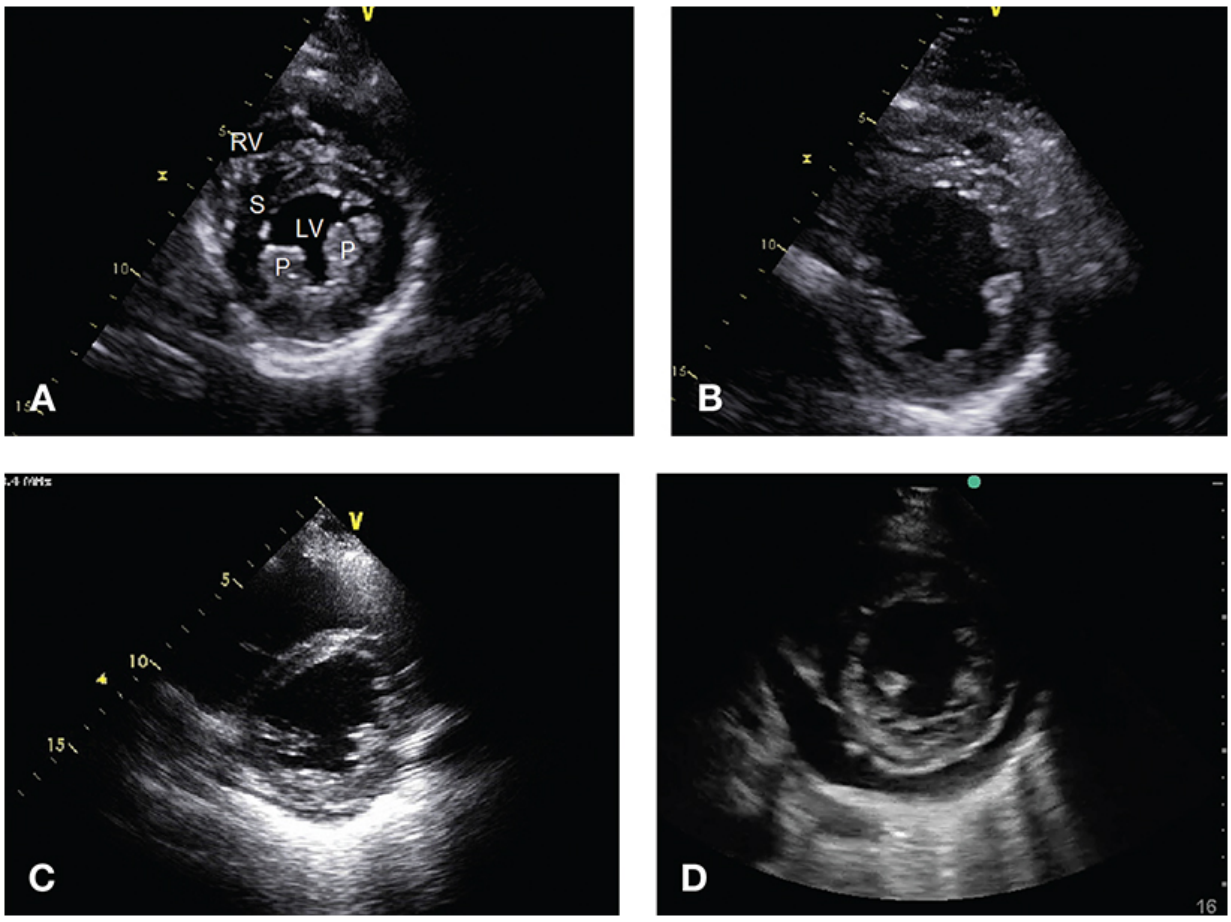


FIGURE 90.9 **A:** Normal PSAX during systole. LV, left ventricle; P, papillary muscle; PSAX, parasternal short axis; RV, right ventricle; S, septum. **B:** Severe left ventricular dysfunction during systole. **C:** Right ventricular overload with flattening of the septum. **D:** Pericardial effusion.

Is There Left Ventricular Dysfunction?

- Dilated cavity with decreased contraction
- Obvious wall motion abnormalities or akinesis, which may be global or in a specific coronary artery distribution

Is There Right Ventricular Overload?

- Large, ovoid-shaped RV
- Septum moves toward LV cavity during early systole, progressing to septal flattening (“D-shaped” LV)

Is the Left Ventricular Hyperdynamic?

- Small LV cavity with touching papillary muscles

Pitfalls of Parasternal Short Axis

- Off-axis evaluation, in which the LV appears elliptical, causes inaccurate assessment of segmental wall movements and septal motion

3. Apical 4 Chamber (A4C)

Image Acquisition

- Probe placed over the cardiac apex at the point of maximal apical pulsation
- Indicator is facing between the patient's left axilla and the bed (about 2-3 o'clock).
- Probe is positioned in line with the long axis of the heart and tilted upward toward the base.
- Depth approximately 14 to 18 cm to image the entire heart, including the atria

Image Optimization

- Deep inhalation may help bring the heart closer to the probe and improve the view.
- Positioning the patient with a left lateral decubitus tilt of the thorax often improves the view.
- Locate the apex of heart made up by the left and right ventricles and center at the top of the screen.
- Slide/rock the transducer until the interventricular septum is centered horizontally in the image and ventricles are fully visualized in their longest axis.
- Rotate until both mitral and tricuspid valves are seen in the same plane.
- Angle transducer superiorly to appreciate the entire heart, including the atria (Figure 90.10).

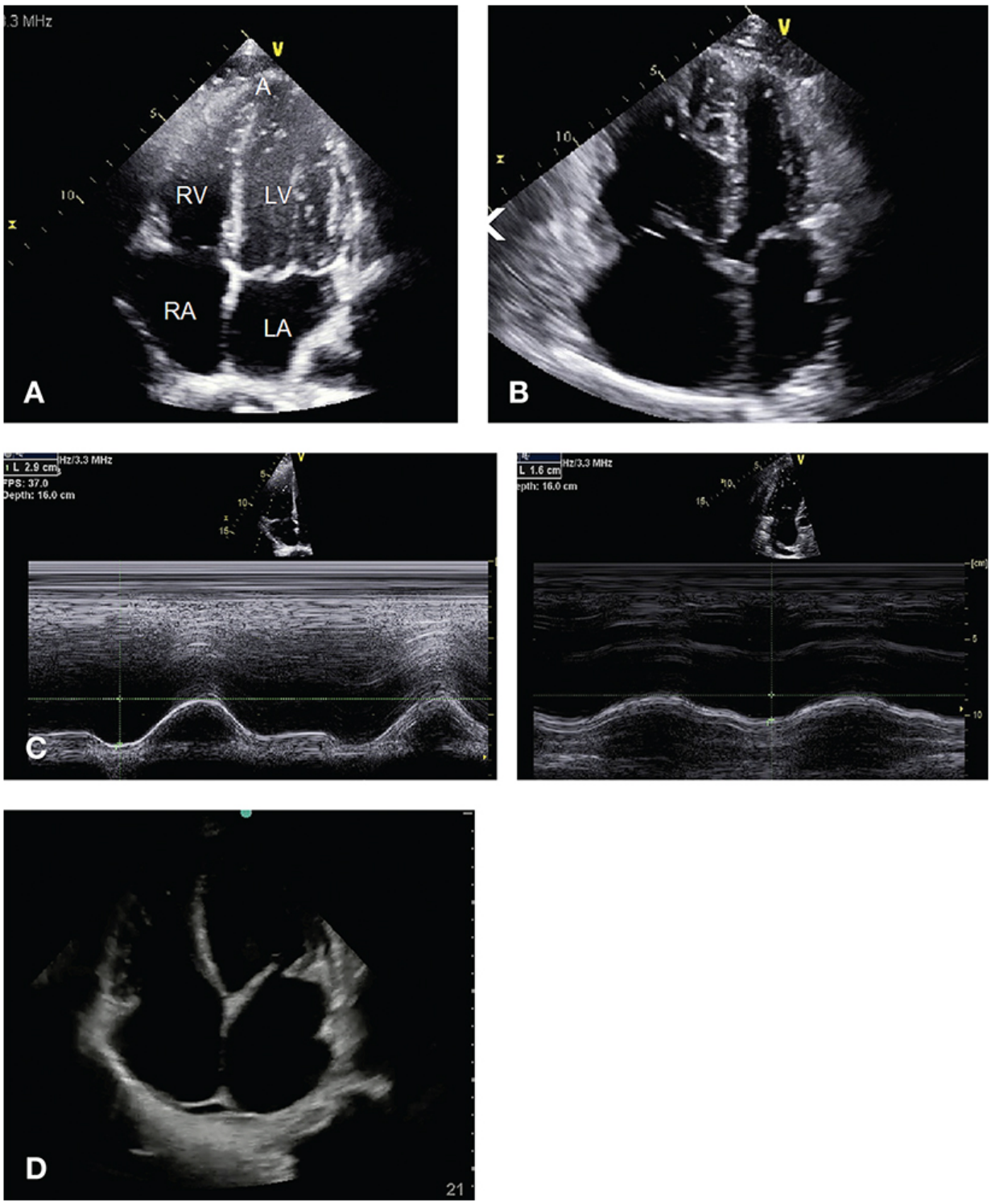


FIGURE 90.10 **A:** Normal apical four-chamber view. A, apex; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. **B:** Right ventricular hypertrophy and dilation. **C:** Example of TAPSE with normal right ventricular function (**left**) and impaired function (**right**). **D:** Left ventricular dilation and dysfunction. TAPSE, tricuspid annular plane systolic excursion.

Normal Structure and Function

- RV is triangular and 2/3 the size of the LV. The majority of the apex is created by the LV.
- RV function: Systolic shortening occurs in the long axis. Tricuspid annular plane systolic excursion (TAPSE) refers to the distance that the lateral annulus of the tricuspid valve moves during systole (M-mode, normal 15-20 mm).
- Mitral and tricuspid valves: open and close normally

Is the Right Ventricle Dilated?

- Moderate dilation: RV 60% to 100% of LV
- Severe dilation: RV larger than LV
- Paradoxical septal movement present

Is There Right Ventricular Dysfunction?

- Decreased free wall motion
- TAPSE less than 15 mm
- McConnell sign denotes hypokinesis or akinesis of the mid-RV free wall and hyperkinesis of the apex

Is There Left Ventricular Dysfunction?

- Dilated chamber with decreased MV opening
- Wall motion abnormalities, which can be global or in a specific coronary distribution

Pitfalls of Apical 4 Chamber

- Challenging view to obtain in a supine patient who is critically ill
- Off-axis imaging: inaccurate assessment of LV/RV function and size
- Endocardium not always visualized, limiting assessment of LV function
- It can be difficult to differentiate between acute and chronic RV volume/pressure overload. Chronic RV dilation is normally associated with hypertrophy of the RV free wall.

4. Subcostal 4 Chamber (S4C)

Image Acquisition

- Gently place the probe under the xiphoid process flat against the patient's abdomen with the indicator pointing toward 3 o'clock.
- The probe is held differently to the other positions, with the hand overlying the probe (Figure 90.7).

Image Optimization

- Apply pressure to keep the probe under the rib cage and tilt upward, bringing the handle of the probe toward the patient's abdomen.
- Direct the beam anteriorly until the heart comes into view, some gentle pressure may be required.
- If bowel gas is obscuring view, move the probe slightly to the left (patient's right) and use the liver as an acoustic window.
- Rotate the probe until the entire LV, including the apex, is visualized (Figure 90.11).

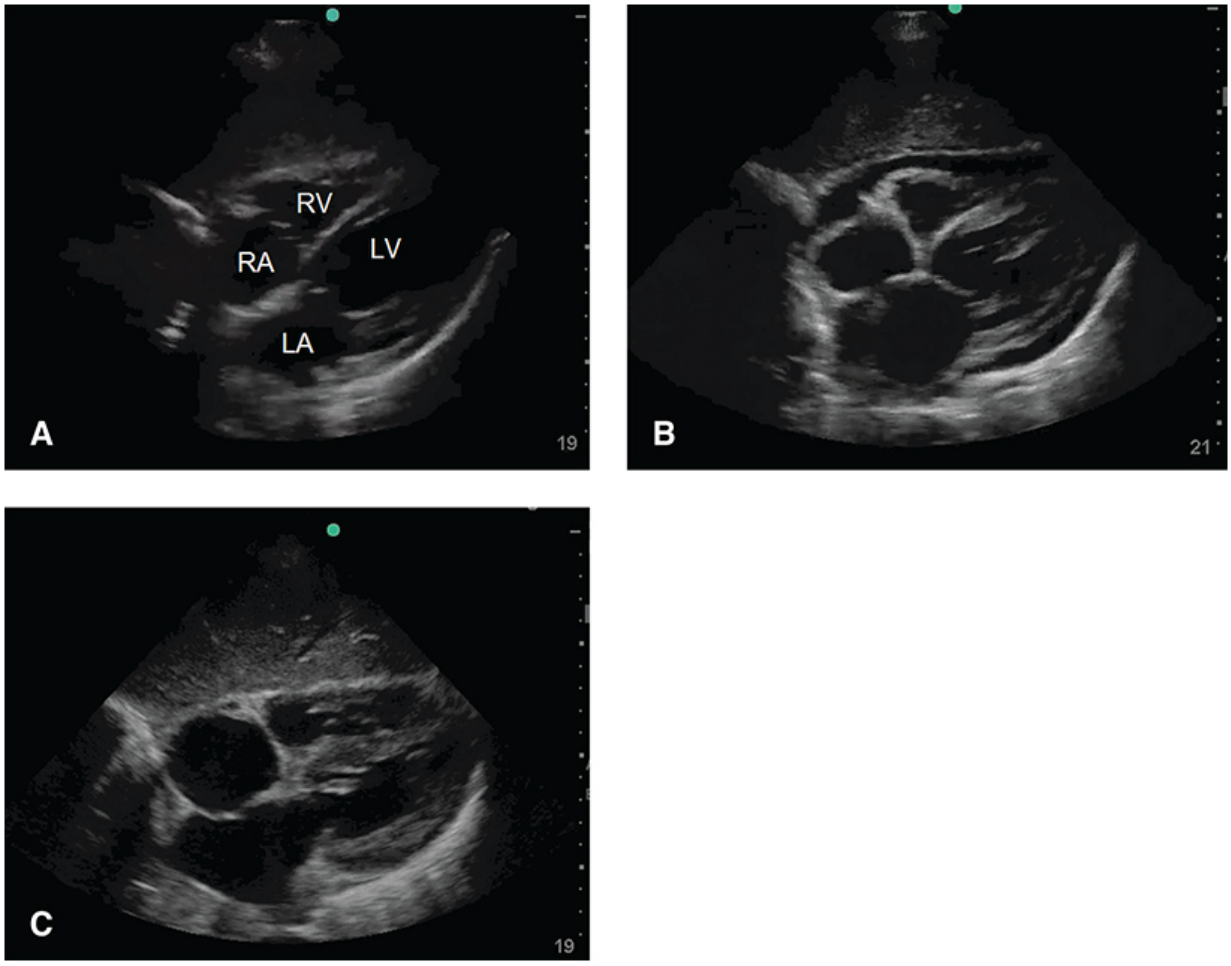


FIGURE 90.11 **A:** Normal subcostal four-chamber view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. **B:** Pericardial effusion. **C:** Right ventricular and left ventricular hypertrophy.

Normal Structure and Function

- Compare size of chambers, LV/RV gross ventricular function, septal motion.

Is There Tamponade?

- Does the pericardial effusion cause right atrial (RA) or RV free wall collapse?

Is There RV Overload?

- RV size, visual TAPSE, septal abnormalities

Pitfalls of Subcostal 4 Chamber

- Off-axis imaging will lead to inaccurate assessment of LV/RV size and function.
- Difficult to obtain in patients with obesity, muscular build, or those who have undergone surgery
- Some patients unable to tolerate the pressure needed to obtain image
- Bowel gas or abdominal distention can be challenging.

5. Subcostal Inferior Vena Cava (SIVC)

Image Acquisition

- Place the probe in the midline, on abdominal preset, with the indicator facing cephalad.
- Angle or slide the transducer until the IVC is seen horizontally across the screen.

Image Optimization

- Rock the probe slightly inferiorly and tilt toward patient's left until IVC is seen entering RA.
- Rotate until IVC traverses horizontally and the hepatic vein is visualized entering the IVC (Figure 90.12).

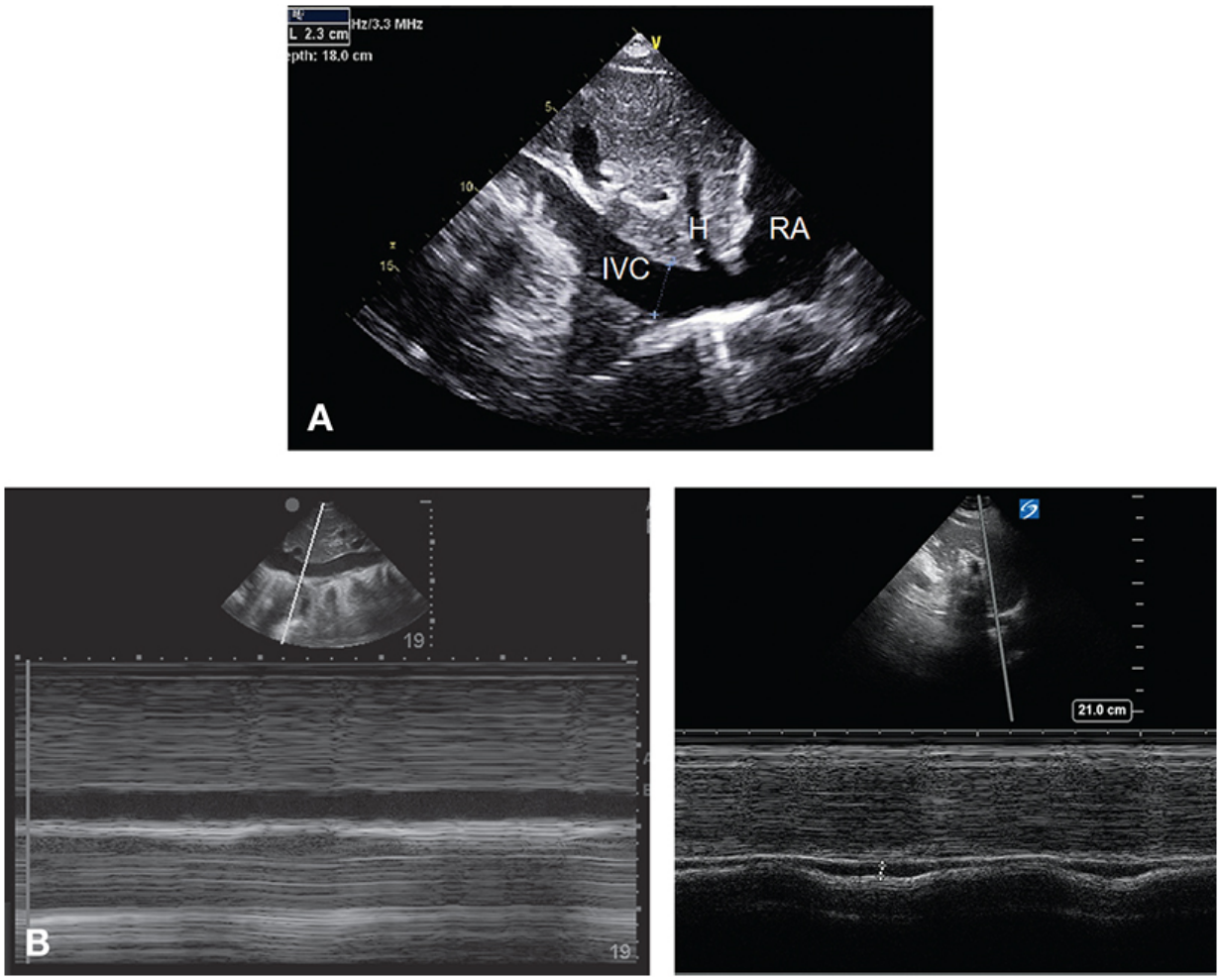


FIGURE 90.12 **A:** Subcostal inferior vena cava (IVC) view. H, hepatic vein; RA, right atrium. **B:** M-mode through the IVC. Dilated IVC without respiratory variation (**left**) compared to small, completely collapsing IVC (**right**).

Normal Anatomy and Function

- Normal IVC size is between 1.5 and 2.5 cm with respiratory variation.
- Increasing age, respiratory effort, and positive pressure ventilation all affect IVC diameter.

Use of Inferior Vena Cava Diameter to Assess Preload

- Caution against solely using IVC diameter to assess volume status. Dynamic echocardiography assessing changes in stroke volume to fluid challenges or a passive leg raise can be considered for advanced users.
- At extremes, IVC diameter may be useful to assess preload responsiveness:
  - If IVC diameter is less than 1.0 cm, patient is likely preload responsive, particularly if they are on positive pressure ventilation.

- If IVC diameter is less than 1.5 cm and exhibits more than 50% collapsibility, patient is likely preload responsive.
- If IVC diameter is more than 1.5 cm but still has more than 50% collapsibility, patient may be preload responsive but need to use other measures of preload responsiveness.
- If IVC diameter is more than 1.7 cm and exhibits less than 50% collapsibility, patient unlikely to be preload responsive.

Pitfalls of Subcostal Inferior Vena Cava

- Limited use in patients on positive pressure ventilation or in respiratory distress
- Aorta can be misidentified as the IVC, especially in a patient experiencing severe hypovolemia, in which the IVC may be very small or completely collapsed. Always identify both the IVC and the aorta.

MEASURING STROKE VOLUME BY BEDSIDE ECHOCARDIOGRAPHY

- The volume of blood traveling through a particular chamber of interest is determined by the following relationship:
  - Volume = **T**ime period of flow × mean **V**elocity of flow × **C**ross-**S**ectional **A**rea of the chamber
- With pulsatile blood flow, when velocity of flow is frequently changing, a velocity time integral (VTI) is used:
  - Volume = VTI × CSA
- VTI is also referred to as the stroke distance in some texts.
- The standard location to measure stroke volume is in the left ventricular outflow tract (LVOT)
- This simple maneuver requires two standard echocardiographic views.

First, the LVOT diameter is measured in the PLAX view, during systole with the aortic valve wide open.

- A caliper is used to measure the diameter of the LVOT at this point. Normal LVOT diameters vary from 1.8 to 2.2 cm.
- Once the LVOT diameter is obtained, it is halved to obtain the radius of the LVOT.
- The cross-sectional area of the LVOT is then obtained by using the following equation:
  - CSA = Πr^2 (Π is 3.14)

The **second view** is an apical five-chamber view, which is a standard apical four-chamber view with a slight upward tilt of the ultrasound beam angle to visualize the LVOT. Pulsed-wave Doppler is then used to obtain a sample from the LVOT, just below the level of the aortic valve.

- The PW Doppler profile at that point is obtained, and the VTI value is calculated as the area under the VTI envelope using standard ultrasound machine software.
- A normal LVOT VTI is 18 to 22 cm.

Stroke volume is obtained by multiplying the VTI by the CSA.

- Serial assessments of VTI are easily obtainable without the need to keep measuring the LVOT diameter; serial VTI measurements can be used as a surrogate for stroke volume to assess response to fluid loading or inotropic support (Figure 90.13).

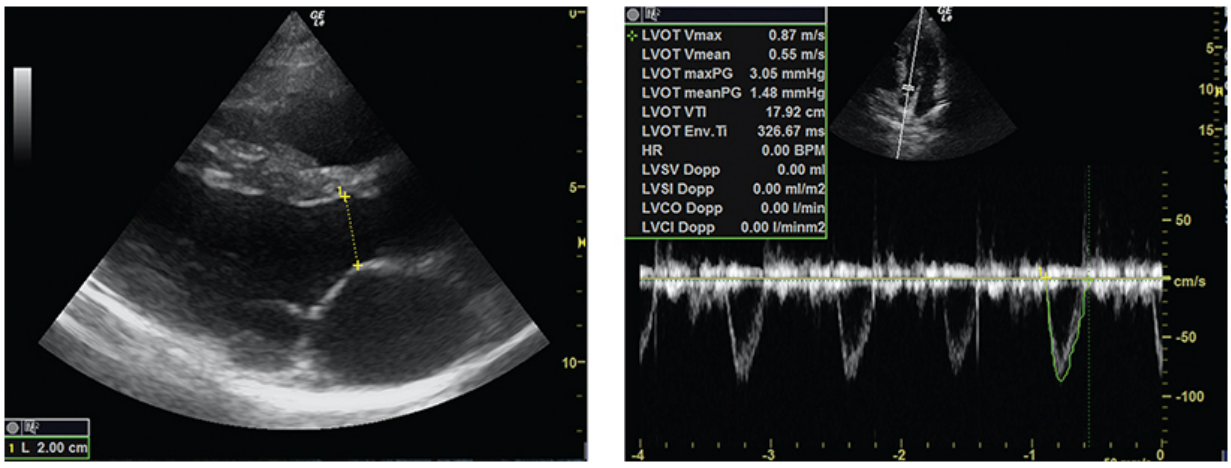


FIGURE 90.13 **LVOT diameter and LVOT VTI to calculate stoke volume**. In this example, stroke volume equals cross-sectional area multiplied by LVOT VTI. LVOT diameter is 2 cm, so cross-sectional area equals 3.14. LVOT VTI is calculated to be 17.92. Stroke volume therefore equals 56 mL. LVOT, left ventricular outflow tract; VTI, velocity time integral.

Shock

Shock is common in the ICU and is associated with high morbidity and mortality. It requires rapid recognition, evaluation, and treatment. Unfortunately, the etiology is not always clear by history and physical examination alone. Point-of-care ultrasound by an experienced user can quickly and accurately differentiate between distributive, hypovolemic, obstructive, and cardiogenic shock. A focused cardiac, lung, and IVC examination takes less than 5 minutes. A complete examination requires a deep vein thrombosis (DVT) screen of the lower extremities (Table 90.3).

TABLE 90.3 **Ultrasound Findings in Different Etiologies of Shock**

	Anterior Lung Examination	Focused Cardiac	IVC	Pitfalls

	Anterior Lung Examination	Focused Cardiac	IVC	Pitfalls
Pneumothorax	Loss of lung slide No B-lines + A-lines		Fixed, dilated	Loss of lung slide not specific for PTX
Tamponade		Pericardial effusion	Fixed, dilated	Difficult to assess hemodynamic significance
Hypovolemic/distributive	Predominantly A-lines	Hyperdynamic LV	Small, collapsing	Other conditions (ie, RV failure) will appear to have hyperdynamic LV
Acute decompensated LV failure	Bilateral B-lines	Depressed LV function	Fixed, dilated	Significant valvular pathologies may not be appreciated
RV pressure/volume overload	A-lines	Large RV, abnormal septal kinetics	Fixed, dilated	Difficult to differentiate between acute and chronic RV failure

IVC, inferior vena cava; LV, left ventricle; PTX, pneumothorax; RV, right ventricle.

1. Using the phased-array probe in the abdominal mode, scan the anterior lung fields looking for lung slide, A-lines, and B-lines.
   - Lung slide? Yes/no
   - A, B, or A/B pattern
2. Switch to the cardiac presets and perform a focused cardiac examination, evaluating overall LV size and function, RV size and function, and presence of pericardial effusion.
   - Pericardial effusion? Yes/no
   - LV function: Hyperdynamic, normal, or moderate/severely depressed?
   - RV size: <2/3 LV or normal septal movement?
   - Finally, evaluate the IVC. A fixed, dilated IVC versus a small, collapsing IVC can help support or rule out certain diagnoses.
   - Fixed and dilated more than 2.5 cm, no respiratory variation
   - Small and collapsing less than 1.5 cm, more than 50% variation with respiration

PNEUMOTHORAX

The presence of lung slide, lung pulse, or B-lines **rules out pneumothorax**. Evaluate multiple areas on the anterior chest of a supine patient to rule out pneumothorax. Absence of lung slide suggests pneumothorax; however, this is not a specific finding. Loss of lung slide is also seen with severe pneumonia/ARDS, prior pleurodesis,

bullous lung disease, examination on the left with a right mainstem intubation, and prolonged apnea. Lung point confirms the diagnosis of pneumothorax but requires enough lung inflation to abut the parietal pleural.

TAMPONADE

Presence of pericardial effusions are often easily identified; however, assessing hemodynamic importance can be difficult. **Hemodynamically significant pericardial effusions will always be associated with a fixed and dilated IVC.** The presence of RV collapse during diastole or RA collapse in systole supports hemodynamic significance. Any questionable pericardial effusion warrants cardiology consultation, and if time allows, evaluation with a more comprehensive echocardiographic examination evaluating for respiratory variation in MV and pulmonary vein inflow velocities.

ACUTE LEFT VENTRICLE FAILURE

LV dysfunction, as a cause of acute hypotension, requires more than just depressed LV function on cardiac ultrasound. Gross visualization of LV contraction and anterior MV excursion are the recommended initial techniques to evaluate overall LV function. Attention should be focused on whether there is segmental decrease in LV function, indicative of a coronary distribution, of if it is global or classic, which could suggest stress-induced cardiomyopathy (apical ballooning and basilar hyperkinesis). Findings should be confirmed in at least two different cardiac views. Acutely decompensated LV failure may have additional ultrasound findings, including bilateral B-lines and a fixed, dilated IVC. If, after full clinical assessment, LV dysfunction is considered to be the cause of the hypotension and poor perfusion (ie, cardiogenic shock), early initiation of dobutamine or mechanical support should be considered. Repeated examinations showing improved LV function and decreased B-line severity, as well as improving stroke volume, can be used to guide interventions such as inotropy, diuresis, and/or afterload reduction.

HYPOVOLEMIC/SEPTIC SHOCK

Both distributive and hypovolemic shock will appear similarly on bedside ultrasound. These patients will have a hyperdynamic LV, predominantly A-line pattern on lung examination, and collapsible IVC. Many times, the LV cavity is obliterated during systole and the endocardial borders appear to be “kissing.” Attention to technique is important as off-axis views may make the LV cavity appear underfilled. It is important to keep in mind other states that will make the LV appear hyperdynamic. These include LV hypertrophy, mitral regurgitation, supraventricular arrhythmias, and decompensated RV failure. Once a hyperdynamic state is observed, other ultrasound findings may be helpful in differentiating between hypovolemia and sepsis. Free fluid in the abdomen can suggest hypovolemia related to acute bleeding or decompensated cirrhosis. Ultrasonographic evidence of an infection, including abscess,

hydronephrosis, or lung consolidation, may suggest sepsis as primary cause. Additional imaging and laboratory testing are often required for a final diagnosis.

RIGHT VENTRICULAR PRESSURE/VOLUME OVERLOAD

The pulmonary circulation in a healthy person is normally a low-pressure, high-capacitance system. The thin-walled RV will dilate with substantial and sustained acute increases in pressure (acute cor pulmonale). The vast majority of patients with PE as a cause of shock will have features of RV dysfunction on point-of-care ultrasound.

RV size and function are best evaluated in A4C, S4C, or PSAX by direct comparison with the LV. In the A4C view, the RV should be triangular and less than 60% of the LV. As the RV enlarges, its shape becomes more ovoid, and it may progress to being the dominant chamber at the apex. Normally, the majority of the apex is made up by the LV.

Septal bowing, bouncing, or paradoxical movement suggests pressure/volume overload of the RV. This is best appreciated in the PSAX view. Septal changes range from septal bouncing to complete flattening (D-shaped LV).

RV function can be assessed by measuring longitudinal movement of the RV free wall at the level of the tricuspid annulus (TAPSE). This can also be assessed visually in the S4C view. In addition, to assess chronicity of any process affecting the RV, the RV free wall can be evaluated with regard to its thickness. A previously healthy RV free wall should not exceed 5 mm in thickness. If the RV free wall is thickened, this would be suggestive of a more chronic process, which has allowed the RV to hypertrophy over time. Another clue to a chronic process would be the elevation of the pulmonary artery systolic pressure (PASP), which is obtained by using CW Doppler analysis of the tricuspid regurgitant jet velocity. Estimated PASP equals $4V^2$, where V is the maximal tricuspid regurgitant jet velocity. The estimated RA pressure based on IVC characteristics is added to this value to estimate the PASP.

An additional finding often seen with acute RV dysfunction is McConnell sign, which refers to hypokinesis or akinesis of the mid-RV free wall and hyperkinesis of the apex. This sign is best seen in the A4C and S4C views. It is not specific for PE and can be seen in ARDS or other conditions associated with acute RV strain.

The ultrasound findings of RV dysfunction are used together with other standard clinical assessments (history, examination, electrocardiogram [EKG] findings, brain natriuretic peptide [BNP], troponin, lactate, chest CT, DVT screen) in patients with evolving acute cor pulmonale from PE. This added risk stratification allows for a reasoned approach to the use of anticoagulation, thrombolytic therapy, inotropic support, and fluid administration.

DEEP VEIN THROMBOSIS

- Traditional duplex and triplex vascular studies include a combination of compression, color, and spectral Doppler.

- Most point-of-care evaluations of DVT used in emergency and critical care settings use the compression portion of the examination only.
- Proximal deep veins of the lower extremities include the external iliac, common femoral, deep femoral, superficial femoral, and popliteal veins.
- Memorization of the venous anatomy and compression points is required in order to perform DVT screening.

Image Acquisition

- A high-frequency transducer is used (5-12 MHz).
- Compared to veins, arteries appear more round, thick-walled, pulsatile, and smaller and require substantial pressure to be compressed. Venous structures generally compress with gentle pressure.
- Ideal patient position is supine with leg externally rotated and knee flexed.
- Start with transducer in transverse position near the iliac artery. The external iliac vessels should be identified here.
- Normal veins should compress fully with complete collapse of the opposing walls. Firm downward pressure is required. Pressure needed to completely collapse the vein is much less than that needed to compress the adjacent artery. Failure to fully compress the vein or the inability to compress the vein without also compressing the adjacent artery suggests the presence of acute thrombus. Acute thrombi are often not visible with ultrasound. Subacute or chronic thrombi, which are organized, will be visible within the vessel lumen.
- **Common femoral vein:** Starting proximal to the greater saphenous vein, slide down the common femoral vein, compressing every 1 to 2 cm. Care must be taken to identify each branching point, until beyond the division into the superficial and deep femoral veins.
- **Popliteal:** Place the transducer in the transverse plane within the popliteal fossa. The popliteal vein is superficial to the artery in the center of the fossa.

Basic Abdomen

KEY POINTS

- The Focused Assessment with Sonography for Trauma (FAST) examination can detect as little as 100 to 260 mL of free peritoneal fluid. The type of fluid cannot be differentiated by ultrasound examination alone.
- Sonographic appearance of injured liver or splenic tissue is subtle and difficult to appreciate. Presence of free peritoneal fluid is a surrogate marker for solid organ injury following trauma.
- Hydronephrosis and bladder outlet obstruction can be rapidly diagnosed with the use of bedside ultrasound, expediting appropriate therapies.

- Identification of renal cysts/masses or bladder masses require further evaluation and are beyond the scope of point-of-care ultrasound.

FREE PERITONEAL FLUID

- The FAST examination evaluates gravitationally dependent areas in the right upper quadrant (RUQ), left upper quadrant (LUQ), and pelvis. This examination was developed to look for hemoperitoneum in trauma patients.
- All types of free fluid, including blood, ascites, bile, lymph, and urine will appear anechoic/hypoechoic. Fluid with higher levels of protein (clotted blood, loculated fluid, pus) are more echogenic.
- Either the curvilinear or phased-array probes may be used.

1. **RUQ:** Evaluate the hepatorenal recess (Morrison pouch), under the diaphragm, and the inferior pole of the kidney (right paracolic gutter).

Image Acquisition

- Place probe in coronal plane (indicator at 12 o'clock) in the mid-axillary line at the level of the xiphoid.
  - Center the hepatorenal recess in the center of the screen.
  - Fluid in the hepatorenal recess will appear as an anechoic space between the two organs.
  - Tilt the probe anteriorly and posteriorly, making sure to evaluate the inferior pole of the kidney.
  - Rock the transducer superiorly to image under the diaphragm.

2. **LUQ:** Evaluate under the diaphragm, the spleen, the splenorenal space, and the left kidney (left paracolic space).

Image Acquisition

- The left kidney is located more posterior and superior compared to the right kidney.
  - Start with the probe in the posterior axillary line as close to the bed as possible (may help to have patient role into right decubitus position if possible).
  - Once the left kidney is centered on the screen, fan the space above and below to evaluate the inferior pole and the splenorenal space.
  - Rock superiorly to appreciate the area under the diaphragm.

3. **Pelvis:** Fluid accumulates in the rectovesicular space or pouch of Douglas in men and women, respectively.

Image Acquisition

- Start with the transducer just above the pubic symphysis in the transverse plane with the indicator toward the patient's right.
- Tilt inferiorly until the bladder is visualized.
- Adjust depth so that the posterior part of the bladder is in the top half of the image.
- Fan through the entire length of the bladder, from the fundus to the neck.
- Rotate 90° and scan the entire bladder in the sagittal plane (Figure 90.14).

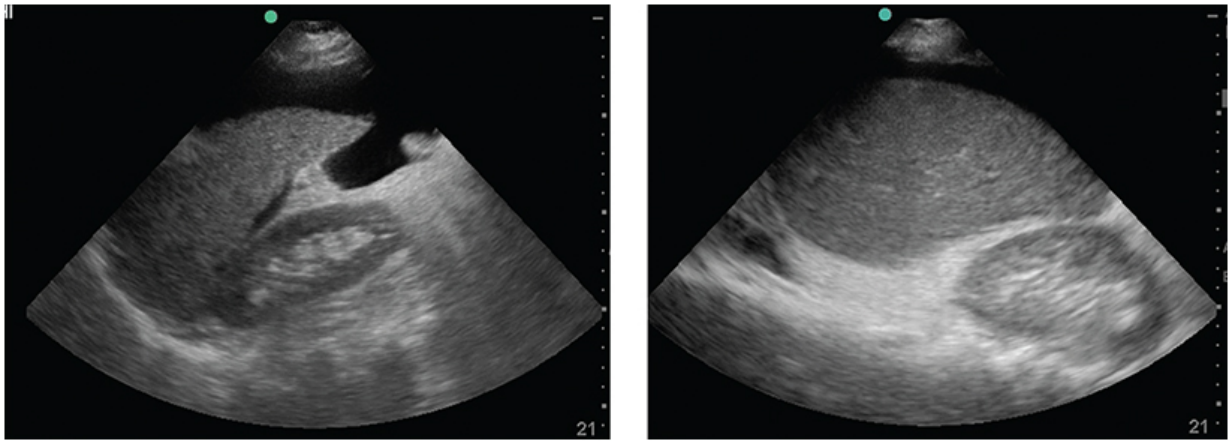


FIGURE 90.14 Free fluid in the right upper quadrant around the liver and within the hepatorenal space (**left**). Free fluid seen around the spleen under the diaphragm in the left upper quadrant (**right**).

RENAL ULTRASOUND

- Normal kidney: Gerota fascia creates a bright outline of the kidney. The underlying renal cortex appears grainy and is slightly less echogenic than surrounding liver or splenic tissue. The renal sinus, which contains the calyces and renal pelvis, appears hyperechoic due to the fat between the renal sinuses. The fluid-filled medullary pyramids and renal calyces appear black.
- The kidneys are positioned slightly obliquely, with the inferior poles more anterior and lateral. Imaging the full length of the kidney requires slight (15°-30°) rotation of the transducer.
- In the longitudinal axis, the kidney appears in the shape of a football. In the transverse, view it is C-shaped.

Image Acquisition

- **Right Kidney:**
  - Place transducer in coronal plane in mid- to anterior axillary line at the level of the xiphoid.
  - Aim the probe slightly posteriorly to visualize the kidney.
  - Center the kidney in the middle of the screen, then rotate counterclockwise 15° to 30° to appreciate the longest axis.

- Assess the entire kidney by tilting the probe anteriorly and posteriorly.
- Rotate 90° to evaluate the short axis.
- Tilt to evaluate the superior and inferior pole.

- **Left Kidney:**
  - Start with the transducer in the posterior axillary line.
  - Center the kidney, rotate 15° to 30° clockwise to find the longest axis, then fan through the kidney.
- Rotate 90° and tilt superiorly and inferiorly to evaluate the entire length of the kidney.

Hydronephrosis

- Differentiated by mild, moderate, and severe:
  - Mild: increased fluid within the calyces with preservation of renal papillae
  - Moderate: rounding of the calyces with ballooning of the papillae. Preservation of the outer cortex
  - Severe: large calyces and pyramids filled with fluid surrounded by thinned cortex
- Compared to renal cysts, in hydronephrosis, all dilated areas of fluid can be traced back to the collecting system.
- Unilateral hydronephrosis is likely secondary to obstructive uropathy and may be associated with pyelonephritis. Differential for obstruction includes ureteral stone or a retroperitoneal mass/adenopathy.
- Bilateral hydronephrosis suggests bladder outlet obstruction, and a sonographic bladder examination should be performed at a minimum (Figure 90.15).

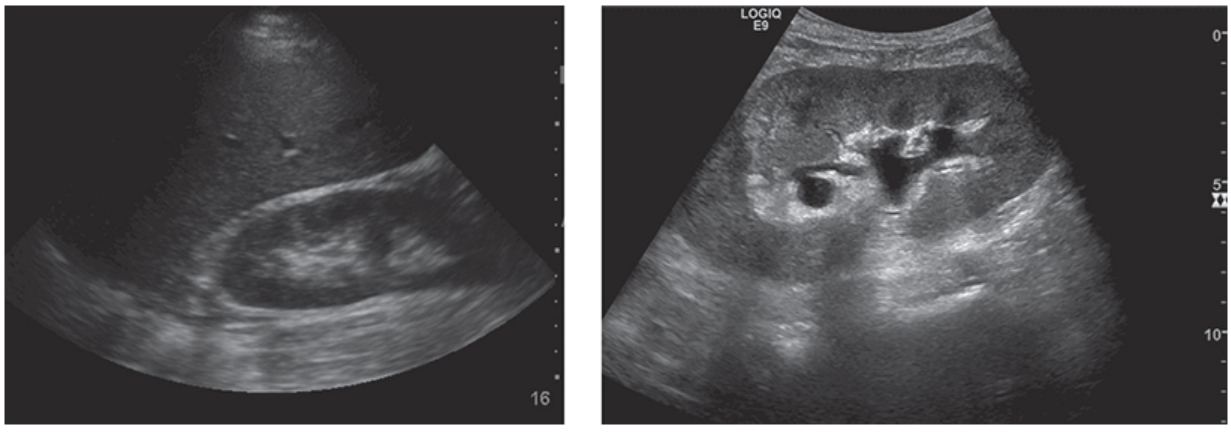


FIGURE 90.15 Normal kidney (**left**). Mild/moderate hydronephrosis (**right**).

BLADDER ULTRASOUND

- Bladder ultrasound can evaluate for bladder distention and enables differentiation between true decreased urine production (empty decompressed bladder) versus

postobstructive renal failure caused by urinary retention (Figure 90.16).

- In patients with declining urine output, this is an invaluable test to assess Foley placement and function.
- Pelvic ascites can mimic the bladder.
- Bladder volume is calculated using measured height, width, and length:
  - Volume = 0.75 × *w* × *h* × 1

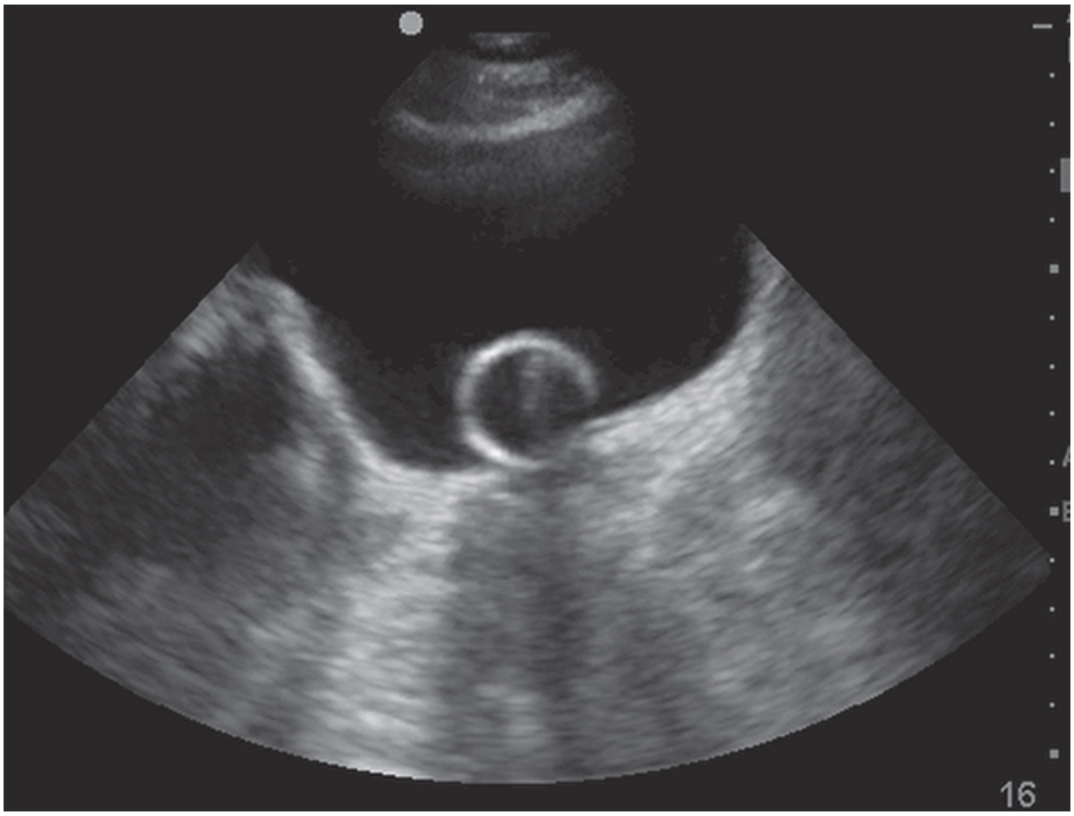


FIGURE 90.16 **Transverse bladder view with distended bladder despite the presence of a Foley catheter (inflated catheter balloon visible).**

Image Acquisition

- Curvilinear probe is recommended since wider footprint allows for visualization of the entire bladder, though phased-array probe is acceptable.
- Place transducer in transverse plane just superior to the pubic symphysis and below the umbilicus.
- Aim transducer inferiorly to appreciate the anechoic, fluid-filled bladder.
- Measure width and length in the transverse plane.
- Rotate probe 90° to evaluate the long axis.
- Measure height in the sagittal (long) axis.

SUGGESTED READINGS

CRITICAL CARE ULTRASOUND

Frankel HL, Kirkpatrick AW, Elbarbary M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients-part I: general ultrasonography. *Crit Care Med.* 2015;43:2479-2502.

Evidence-based guidelines for appropriate use of ultrasonography in the ICU for diagnostic and therapeutic chest, abdomen, pelvic, neck and extremity exams.

Levitov A, Frankel HL, Blaivas M, et al. Guidelines for the appropriate use of bedside general and cardiac ultrasonography in the evaluation of critically ill patients-part II: cardiac ultrasonography. *Crit Care Med.* 2016;44:1206-1227.

Consensus established guidelines for the use of cardiac ultrasonography in the ICU.

Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française statement on competence in critical care ultrasonography. *Chest.* 2009;135:1050-1060.

Consensus statement defining competence in critical care ultrasonography. Competence includes all aspects of pleural, lung, abdominal and vascular image acquisition, image interpretation, clinical applications and specific limitations. Specific technical (image acquisition) and cognitive (image interpretation) elements are described for each exam.

PHYSICS

Bakhru RN, Schweickert WD. Intensive care ultrasound: I. Physics, equipment, and image quality. *Ann Am Thorac Soc.* 2013;10(5):540-548.

Introduction to physical principles of image generation and description of common artifacts.

PULMONARY/RESPIRATORY FAILURE

Lichtenstein DA. BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. *Chest.* 2015;147(6):1659-1670.

Overview of the history of lung ultrasound, followed by a review of the BLUE-protocol to diagnose acute respiratory failure and the FALLS-protocol for undifferentiated shock.

Volpicelli G, Elbarbary M, Blaivas M, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012;38:577-591.

Multi-specialty, international, evidence-based guidelines on the clinical application of lung ultrasound.

FOCUSED ECHOCARDIOGRAPHY

Repessé X, Charron C, Vieillard-Baron A. Intensive care ultrasound: V. Goal-directed echocardiography. *Ann Am Thorac Soc.* 2014;11:122-128.

Describes how to rapidly approach hemodynamically compromised patients using focused cardiac ultrasound.

Via G, Hussain A, Wells M, et al. International evidence-based recommendations for focused cardiac ultrasound. *J Am Soc Echocardiogr*. 2014;27:683.e1-683.e33.

Guidelines from the first international conference on focused cardiac ultrasound (FoCUS) by The World Interactive Network Focused on Critical Ultrasound. An international, multi-disciplinary panel developed comprehensive, evidence-based recommendations for FoCUS.

DVT

Barrosse-Antle ME, Patel KH, Kramer JA, Baston CM. Point-of-care ultrasound for bedside diagnosis of lower extremity DVT. *Chest*. 2021;160(5):1853-1863.

Describes the accepted techniques for DVT examination and provides illustrations with ultrasound images.

VOLUME RESPONSIVENESS/ADVANCED ECHOCARDIOGRAPHY

Narasimhan M, Koenig SJ, Mayo PH. Advanced echocardiography for the critical care physician: part 1. *Chest*. 2014;145(1):129-134.

Explains the principles, limitations, and proper application of the various forms of Doppler ultrasound.

Narasimhan M, Koenig SJ, Mayo PH. Advanced echocardiography for the critical care physician: part 2. *Chest*. 2014;145(1)135-142.

Discusses methods for measuring left heart systolic and diastolic function, right ventricular size and systolic function and ends with a description of a method to assess preload responsiveness.

ABDOMINAL

Kameda T, Taniguchi N. Overview of point-of-care abdominal ultrasound in emergency and critical care. *J Int Care.* 2016;4:1-9.

Review of abdominal ultrasonography in the evaluation of acute abdominal pain, hemoperitoneum, and renal dysfunction.

Boniface KS, Calabrese KY. Intensive care ultrasound: IV. Abdominal ultrasound in critical care. *Ann Am Thorac Soc.* 2013;10:713-724.

Reviews focused trauma (eFAST), kidney and bladder, and abdominal aorta exams. Provides techniques for image acquisition, describes specific limitations, and shows examples of normal and abnormal findings.

SECTION XX END-OF-LIFE ISSUES AND INFORMATICS

91 Patient and Family Engagement, Goals of Care Communication, and End-of-Life Care in the Intensive Care Unit

Brian T. Wessman

Despite individuals' stated preference to die at home, most deaths occur in institutions (hospital or nursing homes). Of those who pass away in hospitals, many die in intensive care units (ICUs) having undergone high-burden interventions despite little likelihood of meaningful benefit. Medicare data show that in the last 6 months of life, one in five beneficiaries will elect to undergo inpatient surgery, and over one-third of patients will have received medical care in the ICU. A staggering one in five patients will die either while in the ICU or soon thereafter. It is estimated that just over 10% of all health care spending in the United States goes toward end-of-life (EOL) care.

Many families of patients receiving critical care services hold overly optimistic expectations regarding survival, functional outcome status, and ultimately the quality of life that is likely to be achieved. Although physicians, in general, have more realistic attitudes, they often still overestimate both functional recovery and survival rates. Poor communication between the medical team and families exacerbates the disconnect between expectations and outcomes. This further complicates the decision-making process and makes it difficult to develop a plan of care likely to meet the expectations of the patient or their families. It has also been shown that physicians have poor comprehension in employing culturally sensitive communication.

To address these problems, critical care providers must have the skills necessary to effectively discuss EOL issues with patients and

their families. Unfortunately, many clinicians are not adequately trained or skilled in discussing the preferences and goals of patients who are critically ill regarding EOL situations. One study showed that although 80% of people say that if they were seriously ill they would want a conversation with their physician regarding EOL care, only 7% of patients actually have this type of conversation. The study to understand prognoses and preferences for outcomes and risks of treatment (SUPPORT) trial documented a number of deficiencies in EOL care in ICUs, including poor communication between physicians and patients about preferences for cardiopulmonary resuscitation (CPR), failure to write do-not-resuscitate (DNR) orders for patients who desire them, and inadequately treated pain and discomfort during the final days of life. Unfortunately, there is little evidence that these problems have been significantly reversed.

Effective EOL discussions can reduce both the incidence of aggressive interventions and the subsequent psychological stress among surviving family members. Furthermore, helping patients and families delineate their life values and preferred care outcomes has been shown to reduce stress among medical providers. Finally, ICU physicians need to have at least a basic understanding of palliative care strategies, as well as the skills and techniques to appropriately manage dying patients. This chapter will review some basic medical ethics, discuss communication strategies to elicit patient-centered goals, delineate some basic palliative care terminology, explore care strategies to support dying patients and their families, and review the concept of medical futility. While this chapter is focused on the unique aspects of the ICU and critical care patient population, the principles and techniques presented are applicable to all medical settings.

Core Ethical Principles

The four traditional pillars of medical ethics are respect for persons, beneficence, nonmaleficence, and justice (Table 91.1). One way physicians can demonstrate respect for persons is by facilitating their

patients' ability to exercise autonomy. Autonomy, derived from the Greek "autos," meaning self, and "nomos," meaning rule, acknowledges the fact that in general, patients are the best arbiters to determine which medical options promote their self-interests and values. An essential part of a physician's duty to respect persons is to provide accurate information and counsel to patients with regard to their illness, potential treatment options, and outcomes. By doing so, the clinician promotes the individual's ability to make autonomous decisions.

TABLE 91.1 Four Traditional Pillars of Medical Ethics

- Autonomy: The capacity to think, decide, and act on one's own free initiative.
- Beneficence: Promoting what is best for the patient.
- Nonmaleficence: Do no harm.
- Justice: Resources are limited; patients in similar situations should have access to the same care.

Beneficence is the positive obligation of an individual to "do good," requiring the clinician to act in patient's best interest. The idea of "what is best" for the patient should be defined from the patient's perspective and informed by competent and complete information provided by the clinician. Beneficence does not always connote a need for intervention. When the benefit of the proposed therapy is not congruent with the patient's goals, beneficence may, in fact, require not intervening. A frequent source of conflict arises between caregivers and patients/families, and within families themselves, when there are significant differences in what each party feels represents the best interests of the patient. This is often most problematic when the patient is unable to participate in the decision-making process.

Nonmaleficence is the principle of "first, do no harm." Virtually all therapies have the potential for adverse effects. Clinicians and patients should always carefully consider the relative harms and

benefits of any intervention. This is especially relevant when providing treatments at the EOL, as curative options are typically not feasible. Particularly careful thought should be given when considering highly invasive, burdensome therapies, such as mechanical ventilation or hemodialysis, during the development of a plan for patients for whom death is imminent, such as someone with terminal widespread metastatic oncologic disease presenting with septic shock.

ICU beds are a scarce resource, and, as such, intensivists are required to make decisions as to who will or will not be admitted to the critical care setting. Justice requires that this resource be allocated fairly, giving consideration to relevant factors such as the condition of the patient, the capabilities of the ICU, and the likelihood that the patient will benefit from intensive care. A decision to provide care to one patient will inevitably have an impact on the ability to treat others. How to fairly allocate ICU resources is a highly controversial issue, a full discussion of which is beyond the scope of this chapter. Nonetheless, physicians should be cognizant of these issues and avoid idiosyncratic decision-making when determining whether or not to admit a patient to the ICU.

Conflicts between these principles will inevitably arise during the care of patients, and these are often more pronounced when treating patients who are critically ill at the EOL. An understanding of the core ethical principles that underlie the practice of medicine can provide the physician with tools to navigate the difficult terrain of guiding patients and families through this highly stressful experience.

Establishing Goals of Care

Establishing appropriate goals of care (GOC) is essential for all aspects of medical care. However, due to the acuity of illness and the potential for rapid disease progression, it assumes even greater importance in the ICU setting. A goal of care is *NOT* the same as a code status or DNR order. Instead, a GOC is a patient-centered value, which may range from a desire for relief from pain to specific

wishes such as “returning home to resume my gardening” or “being able to independently attend a baseball game.” The objective of a GOC discussion is for the health care team to gain an understanding of the patient’s values and preferences and to provide the patient and/or family with accurate prognostic and treatment information. Ideally, together the physician and patient/family can develop an appropriate patient-centered treatment plan, including resuscitation status and degrees of care intervention, that is congruent with this expressed personal quality of life goal.

Patients admitted to ICUs face an increased risk of death and the prospect of being subjected to invasive procedures and treatments. Individual’s preferences for intervention vary widely. Studies have demonstrated that as the potential for a good outcome declines, so does the willingness to undergo highly burdensome treatment regimens. However, individual preferences are not uniform. In one study, 26% of those surveyed stated they strongly agreed with receiving ICU care despite an outcome predicted to be a persistent vegetative state or terminal illness. Conversely, between 1% and 2% did not wish to undergo ICU care even if they were to be returned to a fully functional health status. Given these data, it is essential for health care providers to determine the patient’s desire for aggressive care either prior to admission or early in the course of an ICU stay.

Upon admission to the ICU, the physician should ascertain whether a patient has previously appointed a Durable Power of Attorney for Health Care (DPOA) and/or completed an Advance Directive (AD) or Portable Medical Directives (POLST) form (Table 91.2). The DPOA appoints a specific individual to serve as a proxy for the patient should they lose decision-making capacity, whereas the AD typically specifies the range of interventions that the patient would find acceptable and under what circumstances. Additional national terminology (state dependent) for this process of physician-patient conversation, advance care planning, and medical order is a communication document referred to as a POLST form. This form delineates levels of specific medical interventions for health care management when a patient is seriously ill. If available, these documents should be obtained and their contents discussed

with the patient/family. Ironically, several studies have shown that the presence of an AD had no association with the intensity of care at the EOL. Much of the value of the AD arises from the accompanying discussion between the patient, family, and physician at the time it is written, clarifying patient's preferences. These documents should be reviewed and explored in-depth with each patient and their family upon admission to the ICU. Realistically, an AD *without* in-depth communication about what intensity of medical care each individual desires is of limited utility.

TABLE 91.2 Durable Power of Attorney for Health Care, Advanced Directive, and Portable Medical Orders

- Durable Power of Attorney for Health Care (DPOA): The legal naming of a trusted person to oversee a patient's medical care and the legal ability to make health care decisions for that patient if they are unable to do so.
- Advance Directive (AD): Legal documents that allow a patient to preemptively spell out personal decisions about end-of-life care prior to critical illness. This legal document also serves as a way to document a patient's wishes for family, friends, and health care professionals with the goal of avoiding any confusion during critical illness.
- Portable Medical Orders (POLST): A national recognized communication process and medical form to help patients who are critically ill delineate advanced care planning, advanced medical interventions, and end-of-life wishes.

The majority of patients have none of these documents, and despite the presence of life-limiting illness, many will have not discussed EOL care with either their personal physician or family members. Thus, it may be that these difficult discussions are occurring in the ICU setting for the first time. If the patient is capable of participating, discussions to establish GOC should be held directly with them. The outcome of these discussions should then be shared by the patient and physician together with the patient's family and loved ones, as directed by the patient. If the patient is not decisional

either due to their acute condition or previous underlying disease, the discussion should be held with an appropriate surrogate (see “Surrogate Decision-Making” section).

Due to their acute critical illness requiring an ICU admission, almost all patients admitted to the ICU should have an initial GOC conversation early in the course of their admission. The purpose of this initial discussion is to ascertain the patient and family’s expectations for the acute hospitalization and underlying disease process. The physician should elicit the values, preferences, and wishes of the patient with respect to what they view as an acceptable outcome for their ICU stay. This may range from hoping for a cure to desiring a pain-free death or anywhere in between. Often, patients have multiple seemingly contradictory goals, in which case the physician should take time to help in clarification and prioritization. It is equally important for the physician to provide prognostic information and advise the patient/family on what can reasonably be expected during the hospitalization. A multiprofessional approach of the physician, bedside nurse, and social worker can facilitate a more well-rounded GOC conversation.

Disparities between the goals of the patient/family and medical goals of the physician can be a source of conflict in the ICU. If significant differences are identified, ongoing discussions to identify reasons for the disagreement and reach a consensus are crucial. This often requires multiple subsequent exploratory conversations. Possible reasons may include misunderstandings on the part of the patient or family as to nature of the disease or treatment options, or a failure of the physician to appreciate cultural differences or other values inherent to the individual patient. It is also important to recognize that goals/values may shift during the evolving course of an acute illness. Therefore, as the clinical scenario changes, ongoing discussions to reevaluate the GOC are necessary.

As with any procedure, adequate documentation of these conversations in the medical record should be chronicled. Advanced care planning (ACP) documentation allows multiple ICU team members to have access to the thought process behind these

conversations and creates a narrative record of this process for ongoing reference.

Shared Decision-Making

Shared decision-making (SDM) is of utmost importance when approaching a GOC discussion and for EOL decisions. The responsibility for most major medical decisions should be *shared* between the ICU team and the patient/surrogate. Ideally, the physician provides information about the disease state(s), current treatments, realistic medical feasibility, and prognosis, whereas the patient/surrogate informs the team about the patient's values, quality of life, and treatment preferences. This two-way information sharing should stimulate questions and conversation for both sides. Subsequently, this should lead to the joint deliberation and decision stage where both sides focus on the best available options for the patient, and together agree on a course of action.

The physician bears the responsibility to develop a plan of care that is medically feasible and congruent with the goals and values of the patient, verbally state this plan, and should not hesitate to make recommendations to the family. When discussing EOL care, and particularly resuscitation status, all too often physicians end the conversation with a question, such as "what *do you* want us to do?" or "should we *do everything?*" This unfairly burdens the family with having to make choices for which they may not be equipped or qualified. When discussing resuscitation status, they may feel that they have to actively choose to end their loved one's life. Instead, by focusing on specific patient-centered values and goals, the physician can develop and recommend a treatment plan that may or may not include initiation of life-sustaining interventions or attempts at resuscitation. The plan should be clearly stated to the patient and/or family with sufficient probing to assure understanding. The family is then prompted to voice if they agree with the stated plan. This way, the burden is shifted appropriately from the family to the physician. Again, the goal is to communicate and jointly develop a critical care

medical plan that best respects patient/family values in light of what is medically achievable.

Surrogate Decision-Making

Patients in the ICU are often unable to participate in decision-making due to their acute illness or underlying disease process. In these instances, appropriate surrogates must be identified. If the patient has appointed a specific individual as DPOA, that individual should serve as the primary decision-maker. Oftentimes, a specific individual is not identified. Many, but not all, states have a legal order of surrogacy established (ie, spouse, offspring, or sibling). One should be familiar with the relevant laws of their state. A valid surrogate can be defined as an individual who can faithfully represent the goals, values, and wishes of the patient, act accordingly and in the patient's best interest. Typically, it is presumed that family members are best able to fill this role; however, persons not related to the patient may also serve as valid surrogates. As implied by the definition, the role of the surrogate is to represent the patient's wishes. However, this is often a difficult task and is almost always colored by the surrogate's own values and preferences. Studies on surrogate decision-making have shown that surrogates accurately represent the patient's wishes only 50% to 70% of the time.

The family may choose to appoint one person as spokesperson or may prefer to decide as a group. Not infrequently, there is disagreement among them as to what the patient's wishes would be. It is important that the intensivist works to guide the family and helps them reach consensus. The communication techniques discussed previously are essential in this process. The intensivist should not hesitate to offer a medically feasible plan that is congruent with the stated GOC. Typically, a series of family meetings in which the disputed issues are explored will lead to consensus and resolution. It is often helpful to include nurses, social workers, chaplains, palliative

care consultants, translators (as indicated), and other team members in these discussions.

The standards for surrogate decision-making are (1) stated wishes, (2) substituted judgment standard, and (3) best interest standard (Table 91.3). Stated wishes are exact verbatim treatment preferences the patient had previously expressed to the surrogate. The substituted judgment standard asks the surrogate to guide the team as to what decision the patient would make in this circumstance, essentially asking the surrogate to assume the voice for what the patient would want if they could speak for themselves. If the patient and surrogate have had specific discussions that inform this decision, then this approach may be reasonable. Often, however, no such discussion has taken place leaving the surrogate to speculate. The best interest standard asks the surrogate to help the physician determine whether the proposed treatment is in the best interest of the patient, weighing the potential benefits and burdens of the treatment with what is known about the goals and values of the patient. This standard can also be problematic, as in the absence of specific information; it is difficult to determine what an acceptable outcome is and what level of treatment burden the patient would tolerate for that outcome. Typically, both surrogates and caregivers *underestimate* the willingness of patients to undergo aggressive interventions and *underestimate* the quality of life that patients deem to be acceptable. The intensivist must play an active role in this process of arriving at a consensus medical plan as part of SDM.

TABLE 91.3 Surrogate Decision-Making

Incapacitated patient's wishes are spoken through a surrogate.

- *Stated wishes:* treatment preferences previously expressed by the patient
- *Substituted judgment standard:* surrogate "dons the mental mantle of the patient" and assumes the voice for what the patient would want if they could speak themselves
- *Best interest standard:* surrogate offers thoughts on the treatment course with highest benefit for the patient based on prior interactions without clear

knowledge of what the patient would want

Communication Strategies

Effective, compassionate communication is essential and can be thought of in the same way as an acquired procedural skill, with the language and terminology used being the instruments. As with any procedure, these skills are teachable, require practice to gain competency, and are of paramount importance for the intensivist. Multiple studies have shown that communication with patients/families in the ICU is frequently inadequate. Physicians often dominate these conversations by speaking over two-thirds of the time and use technical language that is not understandable to the listener. One study showed that in approximately 30% of family meetings, physicians miss the opportunity to listen, acknowledge, and address families' emotions, explore individual patient preferences/desires, and explain surrogate decision-making.

Language can be used in a constructive or destructive manner (Figure 91.1). Expressions of compassion and empathy are particularly important. Use positive phrases emphasizing the things you *will do*, such as you "WILL provide comfort, WILL provide pain medications, WILL provide dignity, WILL respect the patient's autonomy," rather than focusing on what you *will not* do, such as "withdrawing care" or "we will not give vasopressors or attempt defibrillation." Phrases such as "Your loved one will not return to the way they were previously …" and "I wish (we could cure the cancer) …" or "I understand how hard this must be for you" help convey clear meaning and show empathy. The author of this chapter prefer the phrase "allow natural death" instead of the commonly employed "do-not-resuscitate (DNR)." This change in terminology can help shift the conversation, as the family understands that the critical care team is allowing the natural progression of life into death. Finally, make sure to include appropriate pauses and listen for the family to offer input.

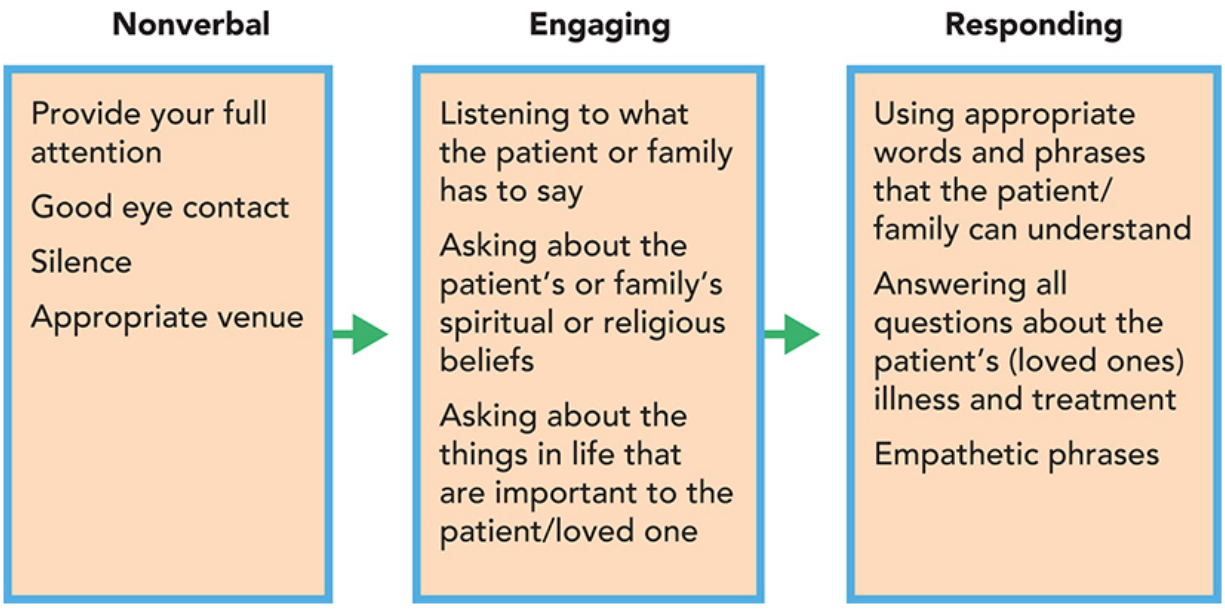

Nonverbal
Provide your full attention
Good eye contact
Silence
Appropriate venue
Engaging
Listening to what the patient or family has to say
Asking about the patient's or family's spiritual or religious beliefs
Asking about the things in life that are important to the patient/loved one
Responding
Using appropriate words and phrases that the patient/family can understand
Answering all questions about the patient's (loved ones) illness and treatment
Empathetic phrases

FIGURE 91.1 Communication is more than language.

It is essential to place the acute situation into the overall context of the patient's illness and life. The patient may have had a prolonged disease course, requiring multiple hospital admissions at increasing frequency over the past months or years. Placing the current acute illness in that context helps the family recognize and accept an inevitable death. In contrast, a previously healthy individual with little to no comorbidity experiencing an acute reversible critical illness is in a fundamentally different situation. Nonetheless, the same strategy and skills are applicable, and the GOC discussion will ideally clarify expectations and assist in the development of an appropriate plan of care.

Surgical and Procedural Considerations

A patient for whom a DNR status has been established may require an invasive procedure for palliative purposes, such as relief of pain secondary to a renal calculus. A proceduralist, such as a surgeon, may be unwilling to intervene on a patient with a DNR unless this established code status is fully reversed. The rationale being that

cardiac arrest during the procedure is often a consequence of the procedure itself or the accompanying anesthesia and would typically be reversible with the appropriate intervention. Furthermore, an existing misconception is that a patient who undergoes a surgical intervention has subsequently agreed on treatment for any/all of the postoperative complications for at least 30 days in the postoperative period.

A patient who undergoes a surgical procedure does not suspend their autonomous right to a specific code status. If the patient requires an invasive or potentially dangerous procedure, the anesthesiologist and the surgeon/proceduralist should hold a "Required Reconsideration" discussion with the patient. This discussion should define the goals of the surgical treatment, potential for resuscitative measures, and potential outcomes without resuscitation. If the patient decides to fully suspend a medical code status decision during the intraoperative/intraprocedure period, a specific timeframe should be defined for reinstating the preexisting code status in accordance with the patient's wishes. If there is any confusion, this should be addressed with the patient/surrogate on arrival to the ICU setting by the critical care medicine team.

Withdrawing and Withholding Life-Sustaining Treatments

Critical care physicians are often faced with decisions to limit life-sustaining treatments (Table 91.4). In one large study of 851 patients admitted to a medical ICU requiring mechanical ventilation, almost 20% had ventilatory support withdrawn. These decisions can be a source of distress and conflict for health care providers and patients and families. Family satisfaction regarding EOL care is higher when families are encouraged to express their thoughts, support structures are in place, when families are assured that their loved one will not be abandoned, and are confident that their loved one will be kept comfortable and not suffer. Furthermore, employing a cultural

assessment, often by an ICU social worker, to identify religious beliefs, determine language barriers (and potential need for a formal translator), and delineate cultural differences should be standard of care.

TABLE 91.4 Limiting Treatments at the End of Life

- Withholding: never starting a medical treatment or therapy
- Withdrawing: stopping a medical treatment or therapy that has already been initiated
- Euthanasia: the intentional killing of a patient (illegal in the United States)
- Physician-assisted suicide: a physician prescribes medication to the patient knowing that the patient intends to use it to commit suicide (legal in only a few states: Washington, Oregon, Vermont, Montana)

The ethical basis for withdrawal of life-sustaining treatments stems directly from the principle of respect for autonomy (see pillars of medical ethics section). It is well-accepted by the medical profession and society at large that an autonomous patient, and therefore by extension their surrogate, may make an informed decision to refuse any proposed treatment, even if the physician believes that such a decision is not in their best interest. From this, it follows directly that patients or their surrogates may opt to discontinue any treatment once initiated. If this were not the case, many patients might be reluctant to initiate potentially beneficial therapies for fear they would not be permitted to stop at a later time. Conflicts may arise when health care providers believe that discontinuation of life-sustaining interventions violates the principles of beneficence and nonmaleficence, or because they feel such actions are in opposition to their own conscience. Alternatively, surrogates may wish to continue aggressive care despite the recommendation of the team that such treatments are only prolonging an inevitable death (see “Futility” section).

Most commonly, withdrawal of life-sustaining treatments is equated with discontinuation of mechanical ventilation. However,

discontinuation of hemodynamic support, hemodialysis, enteral nutrition, transfusions, or other interventions should also be considered in this context. Once the decision to withdraw life-sustaining strategies has been made, all such therapies may be discontinued simultaneously. Alternatively, one published strategy is that of “stuttered withdrawal” or the staggered removal of life-sustaining treatments. In cases of family difficulty with EOL decisions, satisfaction was higher with stuttered withdrawal, as it offered the family time to adjust to the decision. The decision to withdraw life-sustaining treatments should be approached in a manner similar to all other treatment decisions. While the ultimate responsibility lies with the attending intensivist physician, it is particularly important in these circumstances that the opinions of other health care providers are given voice and considered. The goal of withdrawing life-sustaining interventions is to remove treatments that are no longer congruent with the patient’s goals and values, and are therefore no longer appropriate. If the patient is not decisional, it is essential that there has been prior discussions with the surrogate(s) and that they are in agreement with the proposed plan. This should be thoroughly documented in the medical record.

In some appropriate cases, a terminal extubation may allow the patient a period of time to communicate or have meaningful interactions with their family members. Often times, the critical illness is too far advanced or the level of mechanical support too intense to allow for this. Attention to the patient’s comfort is paramount throughout the patient’s ICU stay, but assumes particular importance during the process of withdrawal of life-sustaining treatments for the patient who is critically ill. Reluctance to administer adequate doses of analgesics and sedatives can result in undue and unacceptable levels of suffering to both the patient and surviving family members. There is ethical and legal consensus that, although respiratory depression or hypotension may be foreseeable consequences of these medications, if the intent is to relieve specific symptoms such as pain or dyspnea, it is essential to treat in adequate doses, despite the possibility that death may be hastened. Ethically, the justification for this has been termed the principle of “double effect” (Table 91.5).

TABLE 91.5 The Principle of Double Effect

An action with two possible consequences, one good and one bad, is morally permissible if the action:

1. Is not in itself immoral.
2. Is undertaken only with the intention of achieving the possible good effect, without intending the possible bad effect, even though the bad effect may be foreseen.
3. The action does not bring about the good effect solely by means of the bad effect.
4. Is undertaken for a proportionately grave reason.

Palliative sedation is the goal of providing vigorous preemptive deep sedation to avoid patient suffering when death is imminent. Studies have repeatedly shown that there is no relationship with palliative sedation and "hastening of death." Medication dosing strategies vary considerably depending on the patient. Most commonly, narcotics such as morphine or fentanyl, are given in combination with a benzodiazepine, typically either midazolam or lorazepam. The medications should be liberally administered initially as a bolus, followed by continuous infusion. Each increase in infusion rate should be preceded by an appropriate bolus to allow for a rapid achievement of steady-state levels. Individual patients may have greatly differing medication requirements, depending on their illness and previous exposure to the drugs. Therefore, the dosage needs to be titrated to individual patient needs. It is paramount to confirm patient comfort prior to proceeding with withdrawal of mechanical ventilation. Neuromuscular-blocking agents should never be used (and train-of-four monitoring should be confirmed prior to withdrawal of mechanical ventilation if there was recent chemically induced paralysis), as they do not provide any palliative effect to the patient and make assessment of comfort impossible.

There should be frequent assessment by the nursing and medical staff for comfort as a patient approaches the EOL. Family members can be given the option of being present during the process,

depending solely on their personal preference. Studies have also shown that the personalization of the dying process and implementing tailored patient-centered wishes can improve EOL care. If possible, the monitor screen in the patient's room should be turned off to allow the family to focus on the patient without distraction.

Futility

The issue of medical futility has been a subject of prolonged and intense controversy. Typically, futility debates arise in the ICU when the health care team believes that continued aggressive interventions are highly unlikely to lead to patient survival, yet the patient's surrogate insists that all measures continue. There are also times when disagreements between the various medical teams providing care for a patient occur. Frustration among physicians and other team members may result in a declaration that further treatment is futile, as an attempt to rationalize discontinuation of treatment and justify a unilateral decision. However, this is ethically problematic, and there remains no clear consensus on an approach to futility. Moreover, the vast majority of clinical situations in which these conflicts arise can be favorably resolved by improved communication between the physician, the various consulting services, and the family.

The concept of "futility" arises from the Latin *futilis*, meaning leaky. Greek mythology held that the daughters of Danaus were condemned in Hades to fill a large pond by transporting water in leaky buckets. Futile medical interventions serve no meaningful purpose, no matter how often they are repeated. Bernard Lo provides three specific conditions that define interventions that are futile in the strictest sense:

1. The intervention has no pathophysiologic rationale. An example of this would be the treatment of acute coronary syndrome with an antifungal medication.

2. Cardiac arrest occurs due to refractory hypotension or hypoxemia despite maximal supportive therapy. Performance of CPR in such a circumstance will be ineffective in restoring circulation.
3. The intervention has been tried and already failed in the patient.

Treatments that meet these strict criteria do not need to be provided. However, these are clearly the minority of clinical situations in which futility is discussed. Many other looser futility criteria have been proposed with concepts of quantitative, qualitative, and cost/benefit; however, these concepts are problematic and should be discarded for these conversations. Most of these “futile definitions” rely on subjective determinations of what an acceptable probability of a favorable outcome is or on determinations of quality of life. Instead of stating a “futile intervention,” a preferred term in critical care medicine is “potentially inadvisable treatment.”

Regardless, a strategy that focuses on process and conflict resolution rather than on absolute definitions is more likely to lead to a favorable outcome. Ultimately, it is the process of increased communication between the health care providers and family members that leads to the satisfactory resolution of these difficult situations. We highly discourage unilateral decision-making with regard to limiting life-sustaining care for patients who are critically ill using futility as a rationale for several reasons. First, the criteria are often incorrectly and inconsistently applied, and perhaps most importantly, such action can lead to extreme distress and anger among the surviving family members. This is not to imply that physicians need to be held hostage to unreasonable demands of unrealistic families but that the focus of the intensivist should be on continued communication to reach a plan of care that best represents patient and family values in light of what is medically achievable and acceptable to all parties. Policy statements, from medical organizations such as the American Medical Association (AMA), concerning due process in regards to resolving conflicts about inadvisable treatments do exist, and we encourage the reader to review these individually for further guidance.

Death by Whole Brain Criteria

Individuals who have sustained catastrophic head injuries or other causes of neurologic devastation may be treated in ICUs and pose some unique challenges and issues for the intensivist. As discussed later, these patients may meet the criteria for death; yet appear to be alive to family members due to the presence of continued cardiac activity, ongoing monitoring devices, and other signs of organ function.

In 1981, the Presidents Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended a uniform standard for the determination of death. This stated that “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards.” While death by cardiopulmonary criteria is understood and well-accepted by physicians and lay people alike, declaration of death by whole brain criteria can be more problematic. Many families and religious groups are reluctant to accept this determination.

Determination of death by whole brain criteria requires examination by an experienced physician. Essential elements include confirming that the patient is in deep coma, documenting the absence of brainstem function, establishing the cause of coma and ensuring it sufficiently accounts for the loss of brainstem function, excluding the possibility of recovery of any brain function, and observing the cessation of all brain function for an appropriate period and/or trial of therapy (Table 91.6). Implicit in this process is the exclusion of potentially reversible causes such as drug intoxications, severe metabolic disturbances, infections, and hypothermia as causes for the coma. The definition does not require the use of specialized testing, but in some instances cerebral perfusion scanning may be helpful to document the absence of cerebral blood flow. There are no published time intervals or “waiting periods” for

brain death examinations (however, hospitals may have their own internal guidelines).

TABLE 91.6 Whole Brain Criteria for Death: An Individual With Irreversible Cessation of All Functions of the Entire Brain, Including the Brainstem Is Dead

1. Cerebral functions are absent.
2. Presence of deep coma, cerebral unreceptivity, and unresponsiveness.
   a. Brainstem functions are absent.
   b. Absence of pupillary, corneal, oculocephalic, oculovestibular, oropharyngeal, and respiratory reflexes.
3. Irreversibility is recognized by:
   a. The cause of coma is established and is sufficient to account for the loss of brain function.
   b. The possibility of recovery of any brain function is excluded.
   c. The cessation of all brain functions persists for an appropriate period of observation and/or trial of therapy.

After the determination of death, the family should not be told the patient is “brain dead” as this terminology is confusing to many. Instead, they should be informed that the patient has been pronounced “dead” (similar to telling a family that someone is “dead” after a cardiac arrest). Families may become confused or angry if discussions regarding withdrawal of support or medical therapies are initiated after declaration of death has occurred. All previously initiated life-sustaining treatments, such as mechanical ventilation and vasopressor support, should be withdrawn. This should be communicated to families prior to the formal brain death examination. In some circumstances, the clinician may elect to continue artificial support for a limited time to determine whether the patient is eligible to be an organ donor or to support organs that will be harvested for organ donation (however, it should be made clear that the patient is dead and you are now providing organ supportive

therapies). It is not necessary to provide sedation or analgesia to the patient at this time, as they have expired.

Conclusion

As Hippocrates taught, “the role of the physician is to cure sometimes, treat often, and comfort always.” Physicians caring for the critically ill will continue to face challenges in providing appropriate care for the dying patient and by extension, their families. Many factors, including increases in technology and an aging population, will almost certainly lead to greater numbers of patients dying in ICUs. A basic understanding and application of the pillars of medical ethics is central to the knowledge of an intensivist. It takes time and practice to excel at the use of language required for comprehensive discussions about GOC and EOL issues. Enhanced communication between critical care providers, patients, and families at all stages of the illness is paramount to assuring that an acceptable outcome is achieved.

> *We only get 1 chance to do this well, and the family will always remember these last days …*
>
> —End-of-Life Nursing Education Consortium course

> *While as physicians and caregivers, we move on to care for the next patient, for the family, this is the only time their loved one will die*
>
> —Anonymous

SUGGESTED READINGS

Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at the end of life in the United States: an epidemiologic study. *Crit Care Med.* 2004;32(3):638-643.

92 Informatics in the Intensive Care Unit

Ryan J. McGuire and Andrew P. Michelson

Technologic innovation and health care digitization are immutably transforming care delivery and assessment of patient outcomes. At the center of this transformation is the bedside application of newer technologies that generate large quantities of clinical information and the electronic health record (EHR), which serves as a data aggregation and visualization tool that facilitates complex decision-making. Combined with the increased patient volumes and comorbidity burden, these driving forces have led to a surge in clinical data, making the intensive care unit (ICU) one of the most data rich clinical environments.

The field of Critical Care Informatics has arisen out of the need to integrate these data and transform them from unorganized bits of information into data that are readily understood, clinically actionable, and outcome directed. This chapter will explore the general fields of clinical informatics (CI), the rise of the EHR as the dominant CI tool, the barriers to health information technology (HIT) adoption, and will conclude by discussing opportunities for developing the Smart ICU of the future.

Clinical Informatics

CI is defined by the American Medical Informatics Association as the "the science of how to use data, information and knowledge to improve human health and the delivery of health care services." It is a field distinctly different from information technology and falls under the larger umbrella of biomedical informatics, which includes

translational bioinformatics, clinical research informatics, CI, consumer health informatics, and public health informatics (Figure 92.1). CI arose as a specialty in the 1960s and has had an expanding role over the last half century, with an exponential growth in the amount and types of patient data being collected. Some of these data are discrete, such as vital signs or laboratory values, while other data are more complex, such as cross-sectional imaging and whole-genome sequencing. As datasets become larger, how such elaborate data are translated into knowledge is a growing challenge. The aim of CI is to improve the quality of individual patient care through the aggregation, harmonization, and analysis of these large clinically related datasets and translate this information into actionable knowledge that can be directly applied at the bedside. The purpose of CI, however, is to not just improve therapeutics, but encompasses all disciplines, including diagnostics, prognostication, decision support, information technology lifecycle management, error mitigation, and workflow optimization.

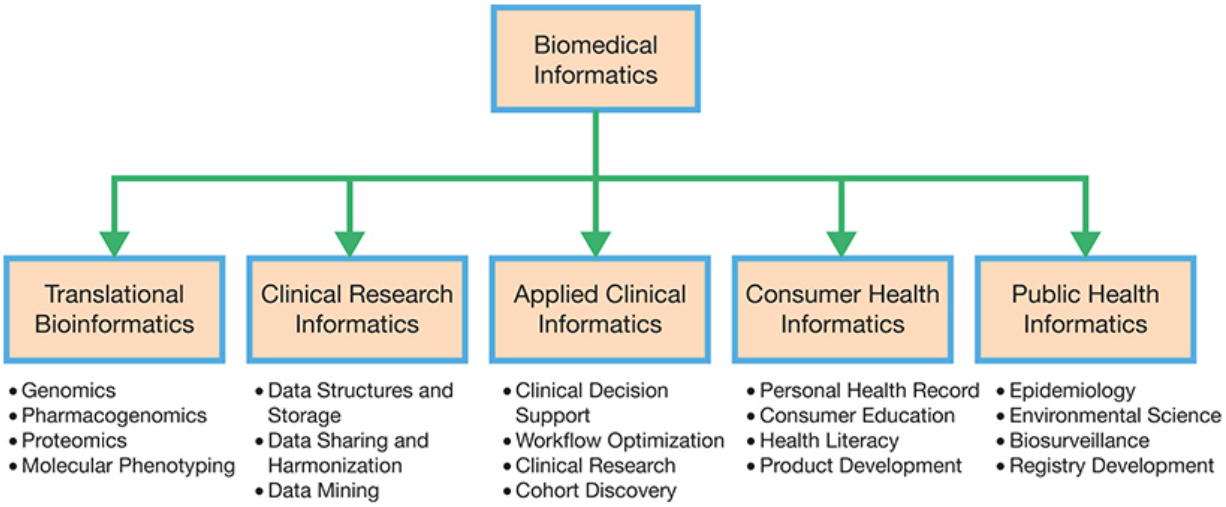


FIGURE 92.1 **Five domains of biomedical informatics.** The core domains of biomedical informatics are shown with their respective key areas of focus listed in bullet points. Although they may appear discrete, there is often significant overlap between these different areas of focus with interdisciplinary collaboration.

The Rise of Health Information Technology

Today, one of the most important pieces of technology used in the ICU is the EHR. It is the digital work environment for health care providers, providing access to historic and current patient information, laboratory and imaging test results, order entry systems, secure communication, data review for research, quality improvement and billing, and other tasks required by health care systems. The first EHRs were used in the early 1970s and were primarily developed by large academic centers. These systems stored their clinical data on central mainframes but were constrained by data storage capabilities, high technologic cost, complicated user interfaces, and singular domain use (inpatient or outpatient). Although these technologic constraints prevented widespread adoption, some of these early systems had advanced features that are still in existence today, such as clinical guideline reminders.

By 2004, only 13% of health care facilities in the United States had adopted a comprehensive EHR, despite more affordable, faster, and higher fidelity computing resources. Seeing success in the digitization of air traffic control and the financial sector, the US government recognized the importance of a digitized health care system and created the Office of the National Coordinator for Health Information Technology. The goal of this agency was to facilitate widespread EHR adoption as a means of preventing medical error and improving quality of care, while at the same time reducing cost and improving efficiency.

Despite the importance and potential positive impact of this initiative, EHR adoption remained low, owing largely to the high upfront capital investment required for implementation. To facilitate this digital health transformation, the Health Information Technology for Economic and Clinical Health (HITECH) act was signed into law as part of the 2009 American Recovery and Reinvestment Act. This piece of legislature infused more than 35 billion dollars into the health care system and provided financial incentives for health care systems to adopt EHRs. More than providing financial assistance to

ameliorate the upfront cost, however, the HITECH act tied financial reimbursement to a set of sequentially more elaborate criteria required for “meaningful use” of an EHR. The criteria for “meaningful use” were set by the Centers for Medicare and Medicaid Services (CMS) and included noteworthy advancements such as computerized physician order entry systems, drug-drug interaction and drug-allergy checkers, e-prescribing, viewing lab and imaging results electronically, and recording clinical notes digitally, among others. Since enactment, the HITECH act has greatly stimulated the adoption of EHRs, going from 12% in 2009 to 96% by 2015.

Building an Integrated Intensive Care Unit

Modern ICUs are designed to leverage technologic devices, which range from automated noninvasive blood pressure monitoring to invasive devices, including ventilators, pulmonary artery catheters, extracorporeal membrane oxygenation machines, and many more. While often overlooked, modern ICUs could not exist without even simple technologic devices such as real-time cardiac telemetry, pulse oximetry, label printers, point-of-care lab devices, and provider workstations. Between all these devices, it is estimated that each ICU patient now generates over 1,200 data points every day. The vast amount of data generated makes connecting, processing, and accessing data from various devices an ever-growing challenge. Moreover, as health care continues to be increasingly digitized, there has been an enormous push to integrate these data across all of health care with the goal of providing better patient care, reducing redundancy, improving outcomes, and lowering cost.

A primary requirement for addressing these challenges is building a strong underlying infrastructure that allows for the connection and communication of these various devices and placing connectivity options throughout patient-care areas to facilitate smooth and seamless data transmission. When several devices are connected, the network must be able to not only accurately identify what data are coming from each device but also the exact time the data were

collected. Therefore, both time synchronization and auto-identification are core to device integration. However, connectivity does not equate to interoperability, as most HIT in the ICU is supplied by different vendors that often use different and proprietary communication and interface protocols.

As a result of these proprietary communication standards, most devices in the ICU do not natively communicate with each other. Instead, interoperability between devices has been built through the expanded use of middleware, which includes servers, data storage, network gateways, and applications that allow for the connection and communication of various hardware and software. Middleware can help transform data into actionable information, remotely monitor multiple devices, operate real-time locating systems, create smart displays, provide decision support, and facilitate hospital administrative and clinical systems. Without middleware, data from each new device would have to be manually charted or viewed, which leads to redundancy, decreased efficiency, and the potential for error.

To combat the growing number of proprietary communication standards and facilitate data integration, the Cures Act of 2016 and its amendment in 2020 (Cures Act Final Rule) led to the creation of the United States Core Data for Interoperability (USCDI). These laws support the development of an interoperable exchange network and established a core set of interoperability standards to which all HIT vendors are required to conform to and is governed by the Office of the National Coordinator for HIT. One of the key standards to arise from this initiative is the HL7 Fast Healthcare Interoperability Resource (FHIR) standard, which as of December 31, 2022, all certified EHR vendors are required to support. The FHIR protocol is an interoperability standard that allows for the transmission of data between EHR vendors, allowing patients to easily access their health information on their personal devices.

While interoperability between health care systems and devices is key to building an integrated ICU, several other limitations have to be addressed before complete integration can be achieved. For instance, despite the real-time capture of high-resolution physiologic

information (arterial waveforms, EKG strips, etc), most of the data generated are not saved or graphically trended in a way that provides meaningful insight. These data storage and harmonization barriers prevent real-time or near-real-time analysis of clinical information. Without advanced storage and analytic platforms to process these data into actionable information, providers are left to make decisions based on “snap shots” in time, which do not accurately reflect the dynamic nature of the patient who is critically ill.

If the allure of informatics is going to come to full fruition, we will need systems that not only report raw data but also store, analyze, interpret, and predict trends to improve the delivery of precision medicine. The challenges facing the establishment of a fully integrated ICU are vast and will require substantial resources from both the government and private sectors before the benefits can be completely realized. Fortunately, several integrated health platforms are being developed, with some already being implemented across the country.

Factors Affecting Health Information Technology Adoption

As technology continues to advance and modern ICUs become increasingly digital, the growing complexity of the modern-day workflow has the potential to lead to uncertainty and hesitation among health care workers and patients. Physicians, advanced practice providers, nurses, support staff, and administration all have different responsibilities to patient care, and how HIT is purchased, implemented, utilized, and upgraded can be viewed positively or negatively depending on the perspective. As a result, several barriers to HIT adoption have been described, and the core obstacles are summarized as follows:

- Increased burnout seen among providers with new deployments or updates to EHR systems

- Reduced efficiency from poorly designed workflows, display of redundant and inconsistent data, and long loading times can limit direct patient interaction and increase medical error
- Inclusion of low-value clerical documentation needed to meet billing requirements resulting in a doubling of clinical note size, without improvements to patient care
- High cost of installing, maintaining, and upgrading equipment and software
- Increased apprehension regarding patient privacy and safety as more personal health information is digitized and health care systems are increasingly partnering with private companies to share clinical data
- Growing concern that advanced analytical techniques such as artificial intelligence and machine learning (AI/ML) can introduce bias and potentially perpetuate discrimination if not adequately trained and validated

As newer and more advanced technologies become more prevalent within ICUs, these issues, in addition to data management and cost, will all need to be addressed if the technologic potential will be realized in the ICU.

Toward a Smart Intensive Care Unit

The ICU of the future will leverage insights derived from disparate data derived from an integrated system of ICUs and provide augmented clinical decision support (CDS) and enhanced automation through a fully EHR-integrated platform. In doing so, knowledge generation will be expedited, and emerging technologies, such as AI/ML, will be implemented to facilitate the translation of protocolized treatments into precision medicine.

CDS tools derived from data captured in the EHR are leading the way toward the Smart ICU of the future through the creation of AI/ML models that utilize discrete and/or radiographic data to predict or

identify clinical outcomes. Early warning systems (EWS), for example, scan medical records looking for impending disease states. One of the most widely published EWS is the TREWScore, a retrospectively developed and prospectively validated ML algorithm that predicts severe-life threatening infections and can improve clinical outcomes by notifying providers and prompting earlier treatment. Similar studies have emerged using EHR data to predict antibiotic resistance at the time of culture collection, successful liberation from mechanical ventilation, and even incorrect provider orders. Other studies leveraging computer vision have created augmented radiographic interpretation systems that can identify correct endotracheal tube positioning, pneumothoraces, and central line malposition within seconds of image collection. While most of these tools show promise in early testing, few have accomplished a clinical implementation or EHR integration, leaving their true performance and clinical impact uncertain.

Beyond CDS, the Smart ICU has the opportunity to enhance efficiency and clinical decision-making by implementing workflow improvement tools such as predictive and prescriptive ordering, templated documenting, and closed-loop medication titration systems (insulin, vasopressors, anti-hypertensives, etc). It can also improve care on a macroscale by providing comprehensive telehealth capabilities, bolstering quality improvement processes, and aggregating data for clinical research.

As health care information technology continues to rapidly advance, it is becoming increasingly important to reimagine healthcare and envision how digital health technologies and informatics can be combined to drive precision medicine.

SUGGESTED READINGS

Adams R, Henry KE, Sridharan A, et al. Prospective, multi-site study of patient outcomes after implementation of the TREWS machine learning-based early warning system for sepsis. *Nat Med*. 2022;28(7):1455-1460.

Anderson DC, Jackson AA, Halpern NA. Informatics for the modern intensive care unit. *Crit Care Nurs Q*. 2018;41(1):60-67.

SECTION XXI APPENDICES

93 Common Equations and Rules of Thumb in the Intensive Care Unit

Rachel K. McDonald

Pulmonary Equations

ALVEOLAR GAS EQUATION

$$P_{AO_2} = F_{IO_2} (PB - PH_2O) - Pa_{CO_2}/R$$

Where P_{AO_2} = alveolar partial pressure of oxygen
F_{IO_2} = fraction of inspired oxygen
PB = barometric pressure (760 mm Hg at sea level)
PH_2O = water vapor pressure
Pa_{CO_2} = partial pressure of carbon dioxide in arterial blood
R = respiratory quotient, assumed to be 0.8

ALVEOLAR-ARTERIAL OXYGEN GRADIENT

$$P_{AO_2} - Pa_{O_2}$$

Normal value is between 3 and 15 mm Hg and is influenced by age. In a healthy 60-year-old person, it may be as high as 28 mm Hg.
For F_{IO_2} = 21%, should be 5 to 25 mm Hg
For F_{IO_2} = 100%, should be less than 150 mm Hg

PARTIAL PRESSURE OF ARTERIAL CARBON DIOXIDE

$$Pa_{CO_2} = K \times V_{CO_2}/[(1 - V_d/V_t) \times VA]$$

Where $PaCO_2$ = the partial pressure of carbon dioxide in arterial blood

K = constant

VCO_2 = carbon dioxide production

V_d/V_t = dead space ratio of each tidal volume breath

VA = minute ventilation

LUNG COMPLIANCE

$$\text{Compliance}_{\text{static}} = \text{Tidal volume}/(\text{Plateau pressure} - \text{PEEP})$$

Where PEEP = positive end-expiratory pressure

Normal compliance in an intubated patient = 0.05 to 0.07 L/cm H_2O

AIRWAY RESISTANCE

$$\text{Airway resistance} = (\text{Peak inspiratory pressure} - \text{Plateau pressure})/\text{Peak inspiratory flow}$$

Normal resistance in an intubated patient is 4 to 6 cm $H_2O \cdot L^{-1} \cdot sec^{-2}$.

DRIVING PRESSURE (DP)

$$DP = P_{plat} - PEEP$$

Where P_{plat} = plateau pressure measured at end inspiration

TRANSPULMONARY PRESSURE (PTP)

$$P_{TP} = P_{alv} - P_{pl}$$

Where P_{alv} = alveolar pressure

P_{pl} = pleural pressure; P_{es} (esophageal pressure) can be used as a surrogate for P_{pl}

Acid-Base Equations

ACUTE RESPIRATORY ACIDOSIS OR RESPIRATORY ALKALOSIS

$$\Delta pH = 0.008 \times (40 - \Delta Paco_2)$$

CHRONIC RESPIRATORY ACIDOSIS OR RESPIRATORY ALKALOSIS

$$\Delta pH = 0.003 \times (40 - \Delta Paco_2)$$

METABOLIC ACIDOSIS

$$\text{Predicted } Paco_2 = 1.5 \times [HCO^-_3] + 8\ (\pm 2) \text{ (Winter's formula)}$$

$$\text{Bicarbonate deficit (mEq/L)} = [0.5 \times \text{body weight (kg)} \times (24 - [HCO^-_3]]$$

METABOLIC ALKALOSIS

$$\text{Predicted } Paco_2 = 0.7 \times [HCO^-_3] + 21(\pm 1.5) \text{ (when } [HCO^-_3] \text{ is } <40 \text{ mEq/L)}$$

$$\text{Predicted } Paco_2 = 0.75 \times [HCO^-_3] + 19(\pm 7.5) \text{ (when } [HCO^-_3] \text{ is } >40 \text{ mEq/L)}$$

$$\text{Bicarbonate excess} = [0.4 \times \text{body weight (kg)} \times ([HCO^-_3] - 24)]$$

VALIDITY OF THE DATA, HENDERSON'S EQUATION FOR CONCENTRATION OF H^+

pH	$[H^+]$ (mmol/L)

pH	$[H^+]$ (mmol/L)
7.60	25
7.55	28
7.50	32
7.45	35
7.40	40
7.35	45
7.30	50
7.25	56
7.20	63
7.15	71

ANION GAP

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO^-_3]) = 10 \pm 4$$

The anion gap should be corrected for albumin, and for every decrease of 1 g/dL in albumin, a decrease of 2.5 mmol in the anion gap will occur.

DELTA GAP

$$\Delta \text{ Gap} = (AG - 12) - (24 - [HCO^-_3]) = 0 \pm 6$$

Positive delta gap signifies a concomitant metabolic alkalosis or respiratory acidosis. Negative delta gap signifies a concomitant normal anion gap metabolic acidosis or chronic respiratory alkalosis.

Renal Equations

CALCULATED OSMOLARITY

$$\text{Osmolarity (mM)} = 2 \times [Na^+] + \frac{\text{BUN (mg/dL)}}{2.8} + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{ETOH}}{4.8}$$

Where ETOH = alcohol

OSMOLAR GAP

Osmolar gap = Measured osmolarity – Calculated osmolarity
(Normal is <10 mOsm.)

ESTIMATED CREATININE CLEARANCE

Cockcroft-Gault CrCl = (140 − age) × (wt in kg) × (0.85 if female)/(72 × Cr)

CREATININE CLEARANCE

$$\text{Creatinine Clearance} = \frac{[\text{Urine creatinine (mg/dL)} \times [\text{Urine volume (mL/day)}]}{[\text{Plasma creatinine (mg/dL)} \times (1{,}440 \text{ min/day})]}$$

FRACTIONAL EXCRETION OF SODIUM ($FENA^+$)

$$FENa^+ = \frac{[\text{Urine } Na^+] \times [\text{Plasma creatinine}]}{[\text{Urine creatinine}] \times [\text{Plasma } Na^+]}$$

FRACTIONAL EXCRETION OF UREA (FE UREA)

$$\text{FE Urea} = \frac{[\text{Urine urea}] \times [\text{Plasma creatinine}]}{[\text{BUN}] \times [\text{Urine creatinine}]}$$

CORRECTING SODIUM FOR HYPERGLYCEMIA

Corrected Na^+ = 0.016 (Measured glucose − 100) + Measured Na

FREE WATER DEFICIT

Free water deficit = TBW × [1 − (Target sodium/Measured sodium)]

Where TBW (total body water in liters) = coefficient × weight in kg
Use coefficient of 0.6 for men, 0.5 for young women and old men, and 0.4 for old women.

USEFUL FORMULA FOR SLOWLY CORRECTING HYPONATREMIA

Expected change in serum sodium with selected infusates

Δ Sodium = (Infusate sodium+ Infusate potassium − Serum sodium)/(TBW + 1)

Where TBW (total body water in liters) = coefficient × weight in kg
Use coefficient of 0.6 for men, 0.5 for young women and old men, and 0.4 for old women.

Hemodynamic Equations

MEAN ARTERIAL PRESSURE (MAP) (70-100 MM HG)

MAP = 1/3 (Pulse pressure) + Diastolic BP (blood pressure)

Where pulse pressure = systolic BP − diastolic BP

ARTERIAL OXYGEN CONTENT (CA_{O_2}) (18-21 ML O_2/DL)

$$Ca_{O_2} = (1.39 \times Hb\ (g/dL) \times Sa_{O_2}) + (0.003 \times Pa_{O_2})$$

MIXED VENOUS OXYGEN CONTENT (CV_{O_2}) (14.5-15.5 ML O_2/DL)

$$Cv_{O_2} = (1.39 \times Hb\ (g/dL) \times Sv_{O_2}) + (0.003 \times Pv_{O_2})$$

ARTERIAL-MIXED VENOUS OXYGEN CONTENT DIFFERENCE (3.5-5.5 ML $_{O_2}$/DL)

$$AVO_2 \text{ difference} = Ca_{O_2} - Cv_{O_2}$$

OXYGEN DELIVERY (ML/MIN) (1,000 ML/MIN)

$$O_2 \text{ Delivery } (D_{O_2}) = CO \times Ca_{O_2} \times 10$$

OXYGEN UPTAKE (ML/MIN) (1,000 ML/MIN)

$$O_2 \text{ Uptake } (V_{O_2}) = CO \times (Ca_{O_2} - Cv_{O_2}) \times 10$$

OXYGEN EXTRACTION RATIO (O_2ER)

$$O_2ER = V_{O_2}/D_{O_2}$$

CARDIAC OUTPUT (CO) (4-7 L/MIN)

$$CO = \text{Heart rate} \times \text{Stroke volume}$$

$$CO \text{ (Fick principle)} = \text{Oxygen consumption}/(Ca_{O_2} - Cv_{O_2})$$

CO in L/min (Fick principle) = Oxygen consumption/[13.4 × Hb × (Sa_{O_2} − Sv_{O_2})]

CARDIAC INDEX (CI) (2.5-4 L/MIN/M^2)

$$CI = CO/BSA$$

Where body surface area (BSA, in m^2) = [height (cm)]$^{0.718}$ × [weight (kg)]$^{0.427}$ × 0.007449

SYSTEMIC VASCULAR RESISTANCE (SVR) (800-1,200 DYNE·S·CM^{-5})

$$SVR\ (dyne \cdot s \cdot cm^{-5}) = 80 \times [(MAP - RAP)/CO]$$

PULMONARY VASCULAR RESISTANCE (PVR) (120-220 DYNE·S·CM^{-5})

$$PVR\ (dyne \cdot s \cdot cm^{-5}) = 80 \times [(mean\ PAP - PAOP)/CO]$$

Point-of-Care Ultrasound Equations

LEFT VENTRICLE STROKE VOLUME (LV SV) (50-120 ML PER CONTRACTION)

$$LV\ SV\ (mL) = LVOT\ CSA \times LVOT\ VTI$$

$$LVOT\ CSA\ (cm^2) = (LVOT\ diameter/2)^2 \times \pi$$

Where LVOT CSA = left ventricular outflow tract cross-sectional area
LVOT VTI = left ventricular outflow tract velocity time integral

STROKE VOLUME INDEX (SVI) (35-50 ML/M^2)

$$SVI = SV/BSA$$

CARDIAC OUTPUT (CO)

$$CO\ (L/min) = LV\ SV \times HR$$

LEFT VENTRICLE FRACTIONAL SHORTENING (LV FS%)

$$LV\ FS\% = [(LVEDD - LVESD)/LVEDD] \times 100$$

Where LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter

RESPIRATORY VARIATION OF INFERIOR VENA CAVA (IVC% COLLAPSIBILITY)

$$IVC\%\ Collapsibility = (D_{max} - D_{min})/D_{max} \times 100$$

Where D_{max}= maximum IVC diameter
D_{min}= minimum IVC diameter

RIGHT VENTRICULAR SYSTOLIC PRESSURE (RVSP)

$$RVSP = 4 \times (TR_{Vmax})^2 + RAP$$

Where TR_{Vmax}= tricuspid regurgitant jet maximum velocity
RAP= right atrial pressure

94 Drug-Drug Interactions

Paul Juang and Scott T. Micek

TABLE 94.1 Cytochrome P450 Enzyme Family Substrates, Inhibitors, and Inducers

1A2	2C9	2C19	2D6	3A4
Substrates				
Acetaminophen Caffeine Clozapine Cyclobenzaprine Imipramine Haloperidol Mexiletine Olanzapine Ondansetron Theophylline Tizanidine (R) Warfarin	Carvedilol Celecoxib Glipizide Ibuprofen Irbesartan Losartan Phenytoin Sulfonylureas Torsemide (S) Warfarin	Amitriptyline Citalopram Clopidogrel Cyclophosphamide Diazepam Imipramine Phenobarbital Phenytoin Proton pump inhibitors Voriconazole	Amitriptyline Aripiprazole Carvedilol Codeine Dextromethorphan Haloperidol Imipramine Lidocaine Metoprolol Metoclopramide Mexiletine Ondansetron Paroxetine Propafenone Propranolol Risperidone Tramadol Venlafaxine	Alprazolam Aripiprazole Aprepitant Apixaban Azole antifungals (except fluconazole) Buspirone Calcium channel blockers Carbamazepine Chlordiazepoxide Clindamycin Clozapine Conivaptan Cyclosporine Diazepam Erythromycin Estradiol Fentanyl Haloperidol Hydrocortisone Ivabradine Ivacaftor and lumacaftor/ivacaftor Ketamine Lefamulin Lidocaine Lurasidone Macitentan

1A2	2C9	2C19	2D6	3A4
				Macrolides (except azithromycin) Meperidine Midazolam Naloxegol Nifedipine Nimodipine PDE-5 inhibitors Protease inhibitors Ranolazine Quetiapine Sirolimus Statins (except pravastatin and rosuvastatin) Tacrolimus Tamsulosin Ticagrelor Tolvaptan Trazodone Verapamil Zolpidem
Substrates				
Inhibitors				
(Increase the Serum and Tissue Concentration of Substrates)				
Amiodarone Cimetidine Ciprofloxacin Clarithromycin Efavirenz Fluvoxamine	Amiodarone Fluconazole Isoniazid Metronidazole Sulfamethoxazole Voriconazole	Cimetidine Fluoxetine Fluvoxamine Isoniazid Ketoconazole Proton pump inhibitors Voriconazole	Amiodarone Bupropion Cimetidine Duloxetine Fluoxetine Haloperidol Methadone Paroxetine Quinidine Ritonavir Sertraline	Amiodarone Aprepitant Azole antifungals (except fluconazole) Cimetidine Clarithromycin Conivaptan Diltiazem Erythromycin Netupitant Protease inhibitors Verapamil
Inducers				
(Decrease the Serum and Tissue Concentration of Substrates)				

1A2	2C9	2C19	2D6	3A4
Carbamazepine Phenobarbital Rifampin Tobacco	Bosentan Carbamazepine Phenobarbital Phenytoin Rifampin	Bosentan Carbamazepine Phenytoin Rifampin	Dexamethasone Rifampin	Bosentan Carbamazepine Efavirenz Glucocorticoids Lumacaftor/ivacaftor Phenobarbital Phenytoin Rifabutin Rifampin St. John's wort

TABLE 94.2 Frequent Drug-Drug Interactions in Patients Who Are Critically Ill

Medication	Interacting Drug	Effect[a]
Cardiac		
Amiodarone	2C9, 2D6, 3A4 substrates (Table 94.1) Sirolimus	↑ Substrate ↑ Sirolimus
Beta-blockers	2D6 inhibitors (Table 94.1)	↑ Beta-blocker
Beta-blockers Carvedilol	Rifampin Phenytoin	↓ Beta-blocker ↓ Beta-blocker
Digoxin	Amiodarone	↑ Digoxin
	Clarithromycin	↓ Digoxin
	Erythromycin	↑ Digoxin
	Quinidine	↑ Digoxin
	Verapamil	↑ Digoxin
Diltiazem/verapamil (3A4 inhibitors)	3A4 substrates (Table 94.1)	↑ Substrate
Lidocaine	Dantrolene Ivabradine Amiodarone	↑ Hyperkalemia, ↓ inotropy effect ↑ Ivabradine ↑ Lidocaine
Antiepileptics		
Carbamazepine (enzyme inducer, 3A4 substrate)	1A2, 2C19, 3A4 substrates (Table 94.1)	↓ Substrate
	Clarithromycin	↑ Carbamazepine

Medication	Interacting Drug	Effect[a]
	Dabigatran	↓ Dabigatran
	Diltiazem	↑ Carbamazepine
	Erythromycin	↑ Carbamazepine
	Lamotrigine	↑ Arrhythmias
	MAOI, serotonergic agents (Table 94.4)	↑ Risk of serotonin syndrome
	Rivaroxaban	↓ Rivaroxaban
	Verapamil	↑ Carbamazepine
Oxcarbazepine	Phenytoin	↓ Oxcarbazepine
Phenytoin (enzyme inducer)	3A4 substrates (Table 94.1)	↓ Substrate
	Amiodarone	↑ Phenytoin
	Canagliflozin	↓ Canagliflozin
	Dexamethasone	↓ Dexamethasone ↓ phenytoin
	Diltiazem/verapamil	↑ Phenytoin
Valproate	Dolutegravir	↓ Dolutegravir
	Edoxaban	↓ Edoxaban
	Lamotrigine	↑ Arrhythmias
	Neuromuscular-blocking agents	↓ Neuromuscular-blocking effect
	Rivaroxaban	↓ Rivaroxaban
	Felbamate	↑ Valproate
	Meropenem	↓ Valproate
Antimicrobials		
Azithromycin	Cyclosporine	↑ Cyclosporine
	Digoxin	↑ Digoxin
	Sirolimus	↑ Sirolimus
	Tacrolimus	↑ Tacrolimus
Carbapenems	Valproic acid	↓ Valproic acid
Clindamycin	Aminoglycosides	↑ Nephrotoxicity
Ciprofloxacin	1A2 substrates (Table 94.1)	↑ Substrate
	Cyclosporine	↓ Ciprofloxacin
	Sucralfate	↓ Ciprofloxacin
	Calcium, iron, antacids	↓ Oral ciprofloxacin
	Tizanidine	↑ Tizanidine

Medication	Interacting Drug	Effect[a]
Antimicrobials		
Clarithromycin (1A2, 3A4 inhibitor)	1A2, 3A4 substrates (Table 94.1)	↑ Substrate
	Digoxin	↑ Digoxin
Linezolid	SSRIs	↑ Serotonin concentrations
	Tramadol	↑ Linezolid
	Tricyclic antidepressants	↑ Linezolid
Piperacillin-tazobactam	Methotrexate	↑ Methotrexate
Vancomycin	Aminoglycosides	↑ nephrotoxicity
Antifungals		
Azole antifungals (except flu/voriconazole) Caspofungin	Acid suppressants Cyclosporine	↓ Azole concentration ↑ Caspofungin
	Dexamethasone	↓ Caspofungin
	3A4 inducers (Table 94.1)	↓ Caspofungin
	Tacrolimus	↓ Tacrolimus
Fluconazole, voriconazole (2C9, 3A4 inhibitor)	2C9, 3A4 substrates (Table 94.1)	↑ Substrate
Itraconazole	3A4 substrates (Table 94.1)	↑ Substrate
Posaconazole	3A4 substrates (Table 94.1)	↑ Substrate
	Ethanol Efavirenz Phenytoin	↑ Posaconazole ↓ Posaconazole (avoid concomitant use) ↓ Posaconazole (avoid concomitant use)
	Rifabutin	↓ Posaconazole (avoid concomitant use)
Antivirals		

Medication	Interacting Drug	Effect[a]
Foscarnet	Ciprofloxacin	↑ Seizures
Others	Clindamycin	↑ Neuromuscular-blocking effect
Neuromuscular-blocking agents	Corticosteroids	↑ Muscle weakness
	Colistin	↑ Neuromuscular-blocking effect
	Inhaled anesthetics	↑ Neuromuscular-blocking effect

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a]↑, Increase serum/tissue concentration; ↓, decrease serum/tissue concentration.From Baniasadi S, Farzanegan B, Alehashem M. Important drug classes associated with potential drug–drug interactions in critically ill patients: highlights for cardiothoracic intensivists. *Ann Intensive Care.* 2015;5(1):44.

TABLE 94.3 Drugs Associated With QT-Interval Prolongation

Antiarrhythmic Agents	
Amiodarone	Procainamide
Disopyramide	Propafenone
Dofetilide	Quinidine
Dronedarone	Quinine
Flecainide	Sotalol
Ibutilide	
Antimicrobials	
Artemisinin derivatives	Foscarnet
Azithromycin	Levofloxacin
Azole antifungals	Moxifloxacin
Chloroquine	Pentamidine
Ciprofloxacin	Primaquine
Clarithromycin	Telavancin
Erythromycin	Terfenadine
Antidepressants	
Amitriptyline	Imipramine
Citalopram	Mirtazapine
Desipramine	Nortriptyline

Doxepin	Sertraline
Escitalopram	Trazodone
Fluoxetine	Venlafaxine
Antipsychotics	
Aripiprazole	Paliperidone
Chlorpromazine	Quetiapine
Clozapine	Risperidone
Droperidol	Sertraline
Fluphenazine	Thioridazine
Haloperidol	Ziprasidone
Lithium	
Other Agents	
Arsenic trioxide	Octreotide
Buprenorphine	Ondansetron
Dolasetron	Ranolazine
Granisetron	Triptan antimigraine meds
Indapamide	Tacrolimus
Methadone	Tizanidine
Metoclopramide	Tyrosine kinase inhibitors

The combination of these agents may increase the risk for adverse arrhythmic event including torsades de pointes.
From Li EC, Esterly JS, Pohl S, Scott SD, McBride BF. Drug-induced QT-interval prolongation: considerations for clinicians. *Pharmacotherapy*. 2010;30(7):684-701.

TABLE 94.4 Drugs With Serotonergic Properties

Increased Release of Serotonin	
Amphetamines and derivatives	MAOIs
Cocaine	Mirtazapine
Levodopa	
Inhibition of Serotonin Metabolism	
Linezolid	Propoxyphene
MAOIs	Selegiline

Impaired presynaptic reuptake	St John wort
Amphetamines and derivatives	SNRIs
Bupropion	SSRIs
Cocaine	St. John wort
Dextromethorphan	Tramadol
Fentanyl	Trazadone
Meperidine Methylene blue	Tricyclic antidepressants
Enhance Serotonergic Effect	
5-HT_3 receptor antagonists (ie, ondansetron)	
Direct Serotonin Receptor Agonist	
5-HT_1 receptor agonists (ie, sumatriptan)	Carbamazepine
Buspirone	Lithium

The combination of these agents may increase the risk for serotonin toxicity manifested by a triad of symptoms, including (1) cognitive changes, (2) autonomic instability, and (3) neuromuscular excitability.

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

From Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis.* 2006;43(2):180-187, with permission.

95 Common Drug Dosages and Side Effects

Lauren Hetzler and Scott T. Micek

TABLE 95.1 Shock

Drug	Dosing	Rare Toxicities	Common Toxicities
Vasopressors/Inotropes (Intravenous)			
Norepinephrine	0.02-3 mcg/kg/min	Tissue hypoxia, tachycardia, arrhythmias, myocardial ischemia, extravasation-associated tissue necrosis	Hyperglycemia
Epinephrine	0.01-1 mcg/kg/min	Arrhythmias, myocardial ischemia, splanchnic and renal hypoxia, lactic acidosis, extravasation-associated tissue necrosis	Tachycardia, hyperglycemia
Phenylephrine	0.5-10 mcg/kg/min	Bradycardia, reduced cardiac output, myocardial ischemia, extravasation-associated tissue necrosis	—
Dopamine	5-20 mcg/kg/min	Myocardial ischemia, tissue hypoxia, extravasation-associated tissue necrosis	Tachycardia, arrhythmias
Vasopressin	0.01-0.08 U/min	Reduced cardiac output, myocardial ischemia, hepatosplanchnic hypoperfusion, thrombocytopenia, hyponatremia, ischemic skin lesions	—

Drug	Dosing	Rare Toxicities	Common Toxicities
Angiotensin II	10-80 ng/kg/min	Arterial and venous thrombosis, tachycardia, peripheral ischemia, hyperglycemia	—
Dobutamine	2.5-20 mcg/kg/min	Arrhythmias	Tachycardia
Milrinone	0.125-0.75 mcg/kg/min	Thrombocytopenia, arrhythmias	Hypotension
Isoproterenol	2-20 mcg/min	Hypotension, hypoxia, acidosis	Arrhythmias
Vasopressors/Inotropes (Oral)			
Droxidopa	100-600 mg PO TID	Supine hypertension, nausea, dizziness	Headache
Midodrine	5-40 mg PO Q8H	Supine hypertension, bradycardia, dysuria	Paresthesias
Corticosteroids			
Hydrocortisone	200 mg/d in four divided doses	—	Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts, HPA axis suppression, increased blood pressure, infection

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

HPA, hypothalamic-pituitary-adrenal; PO, by mouth; TID, three times daily.

TABLE 95.2 Respiratory Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
ARDS, Status Asthmaticus, COPD Exacerbation			

Drug	Dosing	Rare Toxicities	Common Toxicities
Corticosteroids			
Methylprednisolone	1-2 mg/kg/d in one to two divided doses, tapering schedule dependent on disease process	—	Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts, HPA axis suppression, increased blood pressure, infection
Dexamethasone	6-20 mg daily, tapering schedule dependent on disease process		See methylprednisolone
Neuromuscular-blocking agents			
Cisatracurium	1-15 mcg/kg/min IV	Bradycardia, residual muscle weakness	—
Rocuronium	1-20 mcg/kg/min IV	Tachycardia, residual muscle weakness	—
Vecuronium	0.25-2 mcg/kg/min IV	Residual muscle weakness	—
Beta-agonists			
Albuterol	8-16 puffs inhaled Q1H to Q4H	Tachycardia, insomnia, irritability/nervousness, tremor, hyperglycemia, hypokalemia	—
Levalbuterol	1.25-2.5 mg Q1H to Q4H		
Anticholinergics			

Drug	Dosing	Rare Toxicities	Common Toxicities
Ipratropium	Two to four puffs inhaled BID to QID	Dry mucous membranes, tachycardia	—
Pulmonary Hypertension			
Calcium channel blockers			
Diltiazem	120-720 mg/d divided in one to four daily doses depending on formulation	Gingival hyperplasia, exacerbation of angina pectoria or acute MI	Peripheral edema, flushing, headache, dizziness, hypotension
Nifedipine	60-240 mg/d divided in one to four daily doses depending on formulation		
Prostacyclins			
Epoprostenol	2-50 ng/kg/min IV 40-160 mcg/h continuous nebulization	Bleeding	Jaw pain, nausea, headache, flushing, hypotension, tachycardia
Treprostinil	1.25-150 ng/kg/min IV or infusion site pain (SC route) Three inhalations (18 mcg) QID	Bleeding	Jaw pain, nausea, headache, flushing, hypotension, tachycardia, infusion site pain[a]
Treprostinil diolamine	0.375-12 mg/d PO in 2-3 divided doses	Bleeding	Headache, diarrhea, nausea
Iloprost	2.5-5 mcg inhaled six to nine times daily		Nausea, headache, flushing, hypotension, cough

Drug	Dosing	Rare Toxicities	Common Toxicities
Selexipag	200-1,600 mcg BID	Hyperthyroidism	Jaw pain, nausea, headache, diarrhea, flushing
Endothelin antagonists			
Bosentan	62.5-125 mg PO BID	Anemia, hypotension	Hepatotoxicity, headache, flushing, peripheral edema
Ambrisentan	5-10 mg PO daily	Hepatotoxicity, anemia	Peripheral edema, headache, cough
Macitentan	10 mg PO daily	Hepatotoxicity, peripheral edema	Anemia, headache
PDE-5 inhibitors			
Sildenafil	20-80 mg PO TID	Vision and hearing changes	Headache, hypotension, flushing, dyspepsia, diarrhea
Tadalafil	20-40 mg PO daily	Vision and hearing changes	Headache, hypotension, flushing, dyspepsia
Soluble guanylate cyclase stimulator			
Riociguat	1-2.5 mg PO TID	Hypotension, anemia	Headache, dizziness, dyspepsia, nausea, diarrhea
Miscellaneous vasodilator			
Nitric oxide	5-40 parts per million	Methemoglobinemia, elevated nitrogen dioxide	Hypotension
Pulmonary Embolism			
Unfractionated heparin	80 U/kg bolus IV, then 18 U/kg/h IV, adjust to aPTT 1.5-2.5 × control	Heparin-induced thrombocytopenia, hyperkalemia	Bleeding

Drug	Dosing	Rare Toxicities	Common Toxicities
Enoxaparin	1 mg/kg SC Q12H or 1.5 mg/kg Q24H	Heparin-induced thrombocytopenia	Bleeding
Alteplase	100 mg IV over 2 hours	—	Bleeding

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; BID, twice daily; COPD, chronic obstructive pulmonary disease; HPA, hypothalamic-pituitary-adrenal; INR, international normalized ratio; IV, intravenous; MI, myocardial infarction; PO, by mouth; QID, four times daily; SC, subcutaneously; TID, three times daily.

TABLE 95.3 Cardiac Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Acute Myocardial Infarction			
Antiplatelet agents			
Aspirin	162-325 mg PO daily	Tinnitus, anaphylaxis, gastritis	Bleeding, dyspepsia
Clopidogrel	600 mg PO loading dose, then 75 mg PO daily	Thrombotic thrombocytopenic purpura	Bleeding
Prasugrel	60 mg PO loading dose, then 10 mg PO daily	Nausea, thrombotic thrombocytopenic purpura	Bleeding, hypertension, headache
Ticagrelor	180 mg PO loading dose, then 90 mg PO BID	Headache, dizziness, bradyarrhythmias, thrombotic thrombocytopenic purpura, hyperuricemia	Bleeding, dyspnea

Drug	Dosing	Rare Toxicities	Common Toxicities
Cangrelor	30 mcg/kg IV bolus prior to PCI, then 4 mcg/kg/min for ≥2 h or duration of procedure 0.75 mcg/kg/min if bridging to cardiac surgery	—	Bleeding
Abciximab	PCI: 0.25 mg/kg bolus at time of PCI, then 0.125 mcg/kg/min	Thrombocytopenia	Bleeding, hypotension, nausea
Eptifibatide	180 mcg/kg bolus, then 2 mcg/kg/min	Hypotension, thrombocytopenia	Bleeding
Tirofiban	25 mcg/kg over 5 min, then 0.15 mcg/kg/min	Bradycardia, thrombocytopenia	Bleeding
Beta-blockers			
Metoprolol	5 mg IV every 5 min × 3 dose, then 25-50 mg PO every 6-12 h	Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction	Bradycardia, hypotension, fatigue, malaise, cold extremities
Esmolol	500 mcg/kg bolus, then 50-300 mcg/kg/min		
Nitrates			
Nitroglycerin	5-200 mcg/min	—	Headache, flushing, dizziness, hypotension, tachycardia
Isosorbide dinitrate	5-40 mg PO TID		
Isosorbide mononitrate	30-120 mg PO daily		
Fibrinolytics			

Drug	Dosing	Rare Toxicities	Common Toxicities
Alteplase	15 mg IV bolus, then 0.75 mg/kg (up to 50 mg) × 30 min, then 0.5 mg/kg (up to 35 mg) × 60 min (max, 100 mg over 90 min)	—	Bleeding
Reteplase	10 units IV bolus, then 10 units IV bolus 30 min after first dose	—	Bleeding
Tenecteplase	One time bolus: ≤60 kg = 30 mg 61-70 kg = 35 mg 71-80 kg = 40 mg 81-90 kg = 45 mg ≥90 kg = 50 mg	—	Bleeding
Anticoagulants			
Unfractionated heparin	60 U/kg bolus, then 12 U/kg/h, adjust to aPTT 1.5-2.5 × control	Heparin-induced thrombocytopenia, hyperkalemia	Bleeding
Enoxaparin	1 mg/kg SC Q12H	Heparin-induced thrombocytopenia	Bleeding
Dalteparin	120 U/kg SC Q12H		
Argatroban	PCI: 350 mcg/kg bolus, then 25 mcg/kg/min		Bleeding
Bivalirudin	PCI: 0.1 mg/kg bolus, then 0.25 mg/kg/h		
Arrhythmias and Conduction Abnormalities			
Atropine	1 mg IV every 3-5 min	—	Dry eyes, dry mouth, urinary retention, tachycardia

Drug	Dosing	Rare Toxicities	Common Toxicities
Epinephrine	10 mcg IV every 3-5 min	—	Tachycardia, hypertension
Procainamide	17 mg/kg bolus (at 20-50 mg/min) then 1-4 mg/min	Torsade de pointes, agranulocytosis, lupus-like syndrome	Diarrhea, nausea, vomiting
Lidocaine	1-1.5 mg/kg bolus (max 3 mg/kg), then 1-4 mg/min	Confusion, drowsiness, slurred speech, psychosis, paresthesias, nystagmus, muscle twitching, seizures, bradycardia	—
Mexiletine	150-200 mg PO every 8-12 h	Hepatotoxicity, blood dyscrasias	Dizziness, ataxia, nausea, vomiting
Amiodarone	150 mg bolus, then 1 mg/min for 6 h, then 0.5 mg/min for ≥18 h	Heart block, pulmonary fibrosis, hypo/hyperthyroidism, blue-gray skin discoloration, torsade de pointes, corneal microdeposits, optic neuropathy	Bradycardia, hypotension, nausea
Sotalol	80 mg PO BID or 75 mg IV BID, increase dose as tolerated based on QTc prolongation	Hypotension, diarrhea, nausea, vomiting	QTc prolongation, bradycardia, palpitations, dizziness, headache
Adenosine	6 mg IV, if not effective in 1-2 min can give 12 mg, may repeat 12 mg × 1	—	Flushing, lightheadedness, headache, nervousness/anxiety
Calcium channel blockers			
Diltiazem	0.25 mg/kg bolus (may repeat 0.35 mg/kg bolus after 15 min), then 5-15 mg/h	Heart block, exacerbation of angina pectoria or acute MI	**Bradycardia, hypotension, constipation (verapamil > diltiazem)**

Drug	Dosing	Rare Toxicities	Common Toxicities
Verapamil	5 mg bolus (may repeat up to total 20 mg), then 5-15 mg/h		**headache, flushing, edema**
Congestive Heart Failure			
Digoxin	Load: 8-12 mcg/kg; give 50% of load in initial dose, then 25% at 6-12 h intervals × 2 Maintenance: 0.125-0.5 mg/d (Dose should be reduced by 20%-25% when changing from oral to IV)	Arrhythmias, heart block, visual disturbances (blurred or yellow vision), mental disturbances	Bradycardia
ACE inhibitors			
Captopril	6.25-50 mg PO TID	Anaphylaxis, angioedema	Cough, hyperkalemia, hypotension, renal insufficiency
Lisinopril	2.5-40 mg PO daily		
Enalapril	2.5-10 mg PO BID		
Ramipril	1.25-5 mg PO daily		
Aldosterone receptor antagonists			
Spironolactone	12.5-50 mg PO daily	Gynecomastia (spironolactone > eplerenone), hyponatremia	Hyperkalemia
Eplerenone	25-50 mg PO daily		
Loop diuretics[a]			
Furosemide	20-80 mg/d IV/PO in two to three divided doses	Ototoxicity	Hypokalemia, hypomagnesemia, hypocalcemia, orthostatic

Drug	Dosing	Rare Toxicities	Common Toxicities
Torsemide	10-20 mg IV/PO daily		hypotension, azotemia
Bumetanide	0.5-2 mg/d IV/PO in one to two doses		
Hypertensive Emergencies			
Nitroprusside	Usual, 0.25-10 mcg/kg/min	Muscle spasm, thiocyanate and cyanide toxicity	Nausea, vomiting, hypotension, tachycardia
Nicardipine	0-2.5 mcg/kg/min	—	Hypotension, tachycardia, headache, flushing, peripheral edema
Clevidipine	1-32 mg/h	Headache, hypertriglyceridemia	Atrial fibrillation, fever, nausea, insomnia
Labetalol	10-40 mg (max 80 mg) as IV bolus at 10-20 min intervals, then 0.5-2 mg/min if needed	Heart block, bronchoconstriction	Hypotension, bradycardia, nausea, vomiting
Clonidine	0.1-0.3 mg PO BID-TID	—	Drowsiness, dizziness, hypotension, bradycardia, dry mouth
Hydralazine	10-40 mg IV every 4-6 h or 10-75 mg PO TID-QID	Drug-induced lupus-like syndrome, rash, peripheral neuropathy	Hypotension, tachycardia, flushing, headache
Enalaprilat	1.25-5 mg IV Q6H	Anaphylaxis, angioedema	Hypotension, hyperkalemia, renal insufficiency

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects. aPTT, activated partial thromboplastin time; BID, twice daily; IV, intravenous; PCI, percutaneous coronary

intervention; PO, by mouth; QID, four times a day; SC, subcutaneous; STEMI, ST-segment elevation myocardial infarction; TID, three times a day.

[a]Usual starting doses are listed for loop diuretics; dosing is highly variable and much larger doses are often used.

TABLE 95.4 Electrolyte Abnormalities

Drug	Dosing	Rare Toxicities	Common Toxicities
Hyponatremia			
Conivaptan	20 mg IV bolus, then 20 mg over 24 h IV for 2-4 d	Osmotic demyelination syndrome with overcorrection of Na^+, hypotension	Diarrhea, hypokalemia
Hyperkalemia			
Insulin regular (Humulin R)	10-20 units IV (given with 4-5 g of dextrose for every ~1 unit of insulin)	Local skin reactions	Hypoglycemia, hypokalemia, weight gain
Sodium bicarbonate	50 mEq IV	Extravasation-associated tissue necrosis	Metabolic alkalosis, hypernatremia, hypokalemia
Albuterol	10-20 mg nebulized over 30-60 min	Tachycardia, insomnia, irritability/nervousness tremor, hyperglycemia, hypokalemia	—
Sodium zirconium cyclosilicate (Lokelma)	10 g up to 3 times daily	Edema, hypokalemia	—
Calcium gluconate	1 g IV over 2 min	Arrhythmias, phlebitis (chloride > gluconate)	Hypercalcemia, constipation (oral)
Hypercalcemia			
Bisphosphonates			
Pamidronate	60-90 mg IV × 1	Thrombophlebitis; bone, joint, muscle pain, atypical	Fever, fatigue, electrolyte abnormalities

Drug	Dosing	Rare Toxicities	Common Toxicities
Zoledronic acid	4 mg IV × 1	fractures, osteonecrosis of the jaw	
Calcitonin	Initial 4 U/kg IM/SC Q12H, up to 8 U/kg IM Q6H	Allergic reaction	Facial flushing, nausea, vomiting, antibody development
Denosumab	120 mg SC weekly × three doses	Hearing loss, osteonecrosis of jaw, atypical fractures	Nausea, constipation, weakness, fatigue, hypophosphatemia
Hypophosphatemia			
Hyperkalemia (potassium phosphate) Hypernatremia (sodium phosphate)	0.08-0.16 mmol/kg IV over 6 h	—	Hyperphosphatemia, hypocalcemia Hypomagnesemia, hyperkalemia,[a] hypernatremia,[b] diarrhea (oral)

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

IM, intramuscularly; IV, intravenously; mEq, milliequivalents; SC, subcutaneous.

TABLE 95.5 Endocrine Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Hypothyroid			
Levothyroxine	Myxedema coma: 200-400 IV as slow bolus, then 50-100 mcg IV Q24H	Signs and symptoms of hyperthyroidism with excessive doses (tachycardia, angina pectoris, arrhythmias, myocardial infarction, heat intolerance, diaphoresis, hyperactivity)	—
Hyperthyroid			

Drug	Dosing	Rare Toxicities	Common Toxicities
Propylthiouracil[a]	Initial 300-600 mg/d in three divided doses, maintenance 50-300 mg/d in divided doses	Agranulocytosis, aplastic anemia, hepatotoxicity, lupus-like syndrome, hypoprothrombinemia, polymyositis[a]	Rash, arthralgias, fever, leukopenia, nausea, vomiting
Methimazole	Initial 20 mg every 4-6 h, maintenance 5-30 mg/d		
Propranolol	10-40 mg PO Q6H	Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction	Bradycardia, hypotension, fatigue, malaise, cold extremities
SS potassium iodide	One to two drops PO Q12H	Hypersensitivity reactions	Metallic taste, nausea, stomach upset, diarrhea, salivary gland swelling
Adrenal Insufficiency			
Hydrocortisone	100 mg IV Q8H	—	Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts, HPA axis suppression, increased blood pressure, infection
Dexamethasone	10 mg IV prior to ACTH stimulation test		
Fludrocortisone	50-200 mcg PO Q24H	—	Increased blood pressure, edema, hypernatremia, hypokalemia

Drug	Dosing	Rare Toxicities	Common Toxicities
Insulin	—	Local skin reactions	hypokalemia Hypoglycemia, hypokalemia, weight gain

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

ACTH, adrenocorticotropin hormone; HPA, hypothalamic-pituitary-adrenal; IV, intravenous; PO, by mouth.

TABLE 95.6 Oncologic Emergencies

Drug	Dosing	Rare Toxicities	Common Toxicities
Allopurinol	600-800 mg/d PO in two to three divided doses	Nausea, vomiting, hypersensitivity reactions	Rash
Rasburicase	0.1-0.2 mg/kg IV or 3-7.5 mg IV × 1	Hypersensitivity reactions, methemoglobinemia, hemolysis	Nausea, vomiting, fever, headache, rash, diarrhea, constipation, peripheral edema

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

IV, intravenous; PO, by mouth.

TABLE 95.7 Temperature Regulation

Drug Class/Prototypes	Dosing	Rare Toxicities	Common Toxicities
Acetaminophen	325-1,000 mg PO Q4-6H PRN	Hepatotoxicity	Nausea, vomiting
Ibuprofen	200-800 mg PO Q6-8H PRN	Gastric ulceration, bleeding, acute renal failure, increased risk of cardiovascular events	Gastric irritation, nausea
Ketorolac	15-30 mg IV/IM Q6H PRN for up to 5 d		

Drug Class/Prototypes	Dosing	Rare Toxicities	Common Toxicities
Dantrolene	1-2.5 mg/kg IV; may repeat every 5-10 min to max cumulative dose 10 mg/kg	Hepatotoxicity, muscle weakness	Drowsiness, dizziness, diarrhea, nausea, vomiting
Bromocriptine	2.5-5 mg PO BID-TID	—	Headache, dizziness, nausea, constipation, hypotension

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

BID, twice daily; IM, intramuscular; IV, intravenous; PO, by mouth; PRN, as needed; TID, three times a day.

TABLE 95.8 Toxicology

Drug	Dosing	Rare Toxicities	Common Toxicities
Activated charcoal	25-100 g	Bowel obstruction	Vomiting, constipation, fecal discoloration (black)
Naloxone	0.4-2 mg IV every 2 min, up to 10 mg	Abrupt reversal may cause withdrawal symptoms (sweating, agitation, hypertension, tachycardia, nausea, vomiting, cardiovascular events, seizures), pulmonary edema	—
Flumazenil	0.2-0.5 mg IV every 1 min, up to 5 mg	Abrupt reversal may cause withdrawal symptoms (sweating, agitation, hypertension, tachycardia, nausea, vomiting, cardiovascular events, seizures)	Vomiting

Drug	Dosing	Rare Toxicities	Common Toxicities
N-Acetylcysteine	IV 150 mg/kg × 1 h, then 12.5 mg/kg/h × 4 h, then 6.25 mg/kg/h × 16 h	Anaphylactic reactions	Edema, flushing, rash, vomiting
Deferoxamine	1 g IV bolus, then 500 mg IV Q4H × 2 doses	Infusion-related reactions (hypotension, tachycardia, erythema, urticaria) anaphylactic reactions, acute respiratory distress syndrome	Urine discoloration (orange-red)
Fomepizole	15 mg/kg IV bolus, then 10 mg/kg IV Q12H × 4 doses, then 15 mg/kg IV Q12H until ethylene glycol or methanol level <20	—	Headache, nausea

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

IV, intravenous.

TABLE 95.9 Infectious Diseases

Drug	Dosing	Rare Toxicities	Common Toxicities
Antibacterial Agents			
Penicillins			
Ampicillin	2-3 g IV Q4-6H	Anaphylaxis, seizures, hemolytic anemia, neutropenia, thrombocytopenia, drug fever	Diarrhea, nausea, vomiting, rash
Aqueous penicillin G	2-4 million U IV Q4H		
Antistaphylococcal penicillins			
Nafcillin	2 g IV Q4-6H	Anaphylaxis, neutropenia, thrombocytopenia,	Diarrhea, nausea, vomiting, rash

Drug	Dosing	Rare Toxicities	Common Toxicities
Oxacillin	2 g IV Q4-6H	acute interstitial nephritis, hepatotoxicity	
β-Lactam/β-lactamase inhibitors			
Amoxicillin/clavulanate	875 mg PO BID	Anaphylaxis, seizures, hemolytic anemia, neutropenia, thrombocytopenia, *C. difficile* colitis, cholestatic jaundice, drug fever	Diarrhea, nausea, vomiting, rash
Ampicillin/sulbactam	1.5-3 g IV Q6H		
Piperacillin/tazobactam	3.375-4.5 g IV Q6H		
Ticarcillin/clavulanate	3.1 g IV Q4-6H		
Cephalosporins			
Cefazolin	1-2 g IV Q8H	Anaphylaxis, seizures, neurotoxicity, neutropenia, thrombocytopenia, drug fever	Diarrhea, nausea, vomiting, rash
Cefoxitin	1-2 g IV Q4-8H		
Ceftriaxone	1-2 g IV Q12-24H		
Ceftaroline	600 mg IV Q12H		
Cefepime	1-2 g IV Q8-12H		
Ceftazidime/avibactam	2.5 g IV Q8H		
Ceftolozane/tazobactam	1.5-3 g IV Q8H		
Cefiderocol	2 g IV Q8H		
Carbapenems			

Drug	Dosing	Rare Toxicities	Common Toxicities
Imipenem-cilastatin	500 mg-1 g IV Q6-8H	Anaphylaxis, seizures (imipenem > meropenem > ertapenem), *C. difficile* colitis, drug fever	Diarrhea, nausea, vomiting
Meropenem	1 g IV Q8H		
Ertapenem	1 g IV Q24H		
Doripenem	500 mg IV Q8H		
Meropenem-vaborbactam	4 g IV Q8H		
Imipenem-cilastatin-relebactam	1 g IV Q6H		
Glycopeptides			
Vancomycin	15 mg/kg IV Q12-24H	Ototoxicity, nephrotoxicity, Red-man syndrome (unlikely without concomitant nephrotoxins), thrombocytopenia, DRESS syndrome	
Telavancin	10 mg/kg IV Q24H	Nephrotoxicity, QTc prolongation, nausea, vomiting, taste sense altered	Nausea, vomiting
Dalbavancin	1,000-1,500 mg IV once, then 500 mg 1 wk later	Infusion reactions	Nausea, headache
Oritavancin	1,200 mg IV once	Infusion reactions	Nausea, headache
Oxazolidinones			

Drug	Dosing	Rare Toxicities	Common Toxicities
Linezolid	600 mg IV/PO Q12H	More common with long-term use: peripheral and optic neuropathy, myelosuppression, serotonin syndrome Possible with short-term use: lactic acidosis	Diarrhea
Tedizolid	200 mg IV/PO daily	Thrombocytopenia, anemia	Nausea, headache, diarrhea
Lipopeptides			
Daptomycin	4-10 mg/kg IV Q24H	Myopathy, anemia	Diarrhea, constipation, vomiting
Streptogramin			
Quinupristin/dalfopristin	7.5 mg/kg IV Q8H	—	Arthralgia, myalgia, inflammation, pain, edema at infusion site, hyperbilirubinemia
Aminoglycosides			
Amikacin	8 mg/kg IV Q12H or 15 mg/kg extended interval	—	Nephrotoxicity, ototoxicity
Gentamicin	3 mg/kg bolus, then 2 mg/kg IV Q8H or 5-7 mg/kg extended interval		

Drug	Dosing	Rare Toxicities	Common Toxicities
Tobramycin	See gentamicin		
Plazomicin	15 mg/kg IV Q24H		
Fluoroquinolones			
Ciprofloxacin	500-750 mg PO BID or 400 mg IV Q8-12H	Anaphylaxis, QTc prolongation, joint toxicity in children, tendon rupture	Nausea, vomiting, diarrhea, photosensitivity, rash, CNS stimulation, dizziness, somnolence
Levofloxacin	500-750 mg IV/PO Q24H		
Moxifloxacin	400 mg IV/PO Q24H		
Macrolides			
Azithromycin	250-500 mg IV/PO daily	QTc prolongation (erythromycin > clarithromycin > azithromycin), cholestasis	Nausea, vomiting, diarrhea, abnormal taste
Clarithromycin	250-500 mg PO BID		
Erythromycin	250-500 mg PO QID or 0.5-1 g IV Q6H		
Tetracyclines			
Tetracycline	250-500 mg PO TID-QID	Tooth discoloration and retardation of bone growth (in children), renal tubular necrosis, dizziness, vertigo, pseudotumor cerebri	Photosensitivity, diarrhea
Doxycycline	100 mg IV/PO Q12H		
Minocycline	200 mg IV/PO, then 100 mg IV/PO Q12H		

Drug	Dosing	Rare Toxicities	Common Toxicities
Eravacycline	1 mg/kg IV Q12H		
Other antibiotics			
Tigecycline	100 mg bolus, then 50 mg IV Q12H	Photosensitivity, pseudotumor cerebri	Nausea, vomiting, diarrhea
Trimethoprim/sulfamethoxazole	5 mg/kg IV Q8H (based on the trimethoprim component) for severe infections 160 mg PO Q12H	Myelosuppression, Stevens-Johnson syndrome, hyperkalemia, aseptic meningitis, hepatic necrosis	Rash, nausea, vomiting, diarrhea
Metronidazole	500 mg IV/PO Q8H	Seizures, peripheral neuropathy (associated with long-term use)	Nausea, vomiting, metallic taste, disulfiram-like reaction
Clindamycin	600-900 mg IV Q8H	*C. difficile* colitis	Nausea, vomiting, diarrhea, abdominal pain, rash
Antifungal Agents			
Azoles			
Fluconazole	100-800 mg PO/IV daily	Hepatic failure, increased AST/ALT, cardiovascular toxicity, hypertension, edema, QTc prolongation (less with isavuconazonium)	Nausea, vomiting, diarrhea, rash, visual disturbances, phototoxicity
Itraconazole	200 mg IV/PO Q8H × 9 doses, then Q12-24H		

Drug	Dosing	Rare Toxicities	Common Toxicities
Voriconazole	6 mg/kg PO/IV Q12H × 2 doses, then 4 mg/kg PO/IV Q12H		
Posaconazole	300 mg IV/PO Q12H × 2 doses, then 300 mg IV/PO Q24H		
Isavuconazonium	372 mg IV/PO Q8H × 6 doses, then 372 mg IV/PO daily		
Amphotericin B products			
Amphotericin B deoxycholate	0.3-1.5 mg/kg Q24H	Nephrotoxicity (less common with lipid formulations), acute liver failure, myelosuppression, infusion reactions	Acute infusion-related reactions, hypokalemia, hypomagnesemia
Liposomal amphotericin B	3-5 mg/kg IV Q24H		
Echinocandins			
Caspofungin	70 mg IV on day 1, then 50 mg IV Q24H	Hepatotoxicity, infusion-related rash, flushing, itching	—
Micafungin	50-150 mg IV Q24H		
Anidulafungin	200 mg IV on day 1, then 100 mg IV Q24H		
Other Antifungal Agents			

Drug	Dosing	Rare Toxicities	Common Toxicities
Flucytosine	25 mg/kg PO Q6H	Myelosuppression, hepatotoxicity, confusion, hallucinations, sedation	Nausea, vomiting, diarrhea, rash
Antiviral Agents			
Nucleoside analogs			
Acyclovir	400 mg PO TID or 5 mg/kg IV Q8H	Nephrotoxicity, rash, encephalopathy, inflammation at injection site phlebitis	Bone marrow suppression,[b] headache, nausea, vomiting, diarrhea (with oral forms)
Valacyclovir[b]	500-1,000 mg PO Q8H		
Ganciclovir[b]	5 mg/kg IV Q12H		
Valganciclovir	900 mg PO daily- BID		
Neuraminidase inhibitors			
Oseltamivir	75 mg PO BID	Confusion, hallucinations	Nausea, vomiting
Zanamivir	10 mg inhaled Q12H	Bronchospasm	Nausea, cough, local discomfort
Peramivir	600 mg IV once	Hypersensitivity reactions, neuropsychiatric effects, hyperglycemia, transaminitis	Diarrhea, neutropenia
Other antiviral agents			

Drug	Dosing	Rare Toxicities	Common Toxicities
Amantadine	100 mg PO BID	Impulse control disorders (pathological gambling), increased libido, livedo reticularis	CNS disturbances (insomnia, agitation), orthostatic hypotension, peripheral edema, xerostomia, constipation
Rimantadine	100 mg PO BID	CNS disturbances	Nausea, vomiting, anorexia, xerostomia
Cidofovir	5 mg/kg IV weekly plus probenecid 2 g PO 3 h before the infusion and then 1 g at 2 and 8 h after the infusion	Anemia, neutropenia, metabolic acidosis, fever, rash	Nephrotoxicity, uveitis/iritis, nausea, vomiting
Foscarnet	40-90 mg/kg IV Q8-24H	Seizures, anemia, fever	Nephrotoxicity, electrolyte abnormalities (hypocalcemia, hypomagnesemia, hypokalemia, hypophosphatemia), nausea, vomiting, diarrhea, headache
Remdesivir	200 mg IV once, then 100 mg IV daily		ALT and AST increase, nausea, bradycardia

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

AST/ALT, aspartate aminotransferase/alanine aminotransferase; BID, twice daily; *C. difficile, Clostridium difficile*; CNS, central nervous system; IV, intravenous; PO, by mouth; QID; four times daily; TID, three times a day; U, units.

TABLE 95.10 Hepatic Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Lactulose	20-30 g (30-45 mL) PO to maintain 2-3 soft stools/day	—	Diarrhea, flatulence, nausea
Neomycin	500-2,000 mg PO Q6-12H	Nephrotoxicity, neurotoxicity	Nausea, vomiting, diarrhea, irritation or soreness of mouth or rectal area
Rifaximin	550 mg PO BID		Peripheral edema, nausea, dizziness, fatigue
Propranolol	20-80 mg PO Q12H	Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction	Bradycardia, hypotension, fatigue, malaise, cold extremities
Nadolol	20-80 mg PO Q24H		
Spironolactone	12.5-100 mg PO Q24H (in a ratio of 100 mg spironolactone: 40 mg furosemide)	Gynecomastia, hyponatremia	Hyperkalemia

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

BID, twice daily; PO, by mouth.

TABLE 95.11 Gastrointestinal Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Proton Pump Inhibitors			
Pantoprazole	20-40 mg PO Q12-24H	Headache, dizziness, somnolence, diarrhea,	—
Esomeprazole	20-40 mg PO Q12-24H		

Drug	Dosing	Rare Toxicities	Common Toxicities
Omeprazole	20-40 mg PO Q12-24H	constipation, nausea	
Lansoprazole	30-60 mg PO Q12-24H		
Other Agents			
Octreotide	50 mcg IV bolus, then 50 mcg/h infusion	Arrhythmias, conduction abnormalities, hypothyroidism, cholelithiasis (long-term use)	Diarrhea, flatulence, nausea, abdominal cramps, bradycardia, dysglycemia
Terlipressin	Days 1-3 administer 0.85 mg IV every 6 h Day 4: If SCr has decreased by at least 30% from baseline, continue 0.85 mg IV every 6 h. If SCr has decreased by <30% from baseline, 1.7 mg IV every 6 h. Maximum of 14 d	Respiratory failure	Abdominal pain, nausea, diarrhea

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

IV, intravenous; PO, by mouth.

TABLE 95.12 Neurologic Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Status Epilepticus			
Lorazepam	4 mg IV × 1, may repeat dose	Paradoxical excitation, hypotension, respiratory depression (high doses)	CNS depression
Midazolam	0.2 mg/kg IM bolus (max 10 mg)		

Drug	Dosing	Rare Toxicities	Common Toxicities
Phenytoin	20 mg/kg IV bolus (max infusion rate 50 mg/min) Maintenance: 5-7 mg/kg day divided in two to four doses	Arrhythmias, hypotension, bradycardia, purple glove syndrome, phlebitis, rash, fever, bone marrow suppression, Steven-Johnson syndrome, hepatitis, gingival hyperplasia, hirsutism, vitamin D deficiency	Concentration-dependent: nystagmus, diplopia, ataxia, sedation, lethargy, mood/behavior changes, coma, seizures
Fosphenytoin	20 mg phenytoin equivalents/kg IV (max infusion rate 150 mg phenytoin equivalents/minute)		
Phenobarbital	20 mg/kg IV bolus (max infusion rate 100 mg/min)	Rash, bone marrow suppression	Sedation, nystagmus, ataxia, nausea, vomiting IV form: hypotension, bradycardia, respiratory depression
Propofol	20 mcg/kg/min	Pancreatitis, propofol infusion syndrome	Hypotension, bradycardia, CNS depression, hypertriglyceridemia
Levetiracetam	60 mg/kg IV bolus Maintenance: 500-1,000 mg IV/PO Q12H	Behavioral disturbances	Somnolence, nausea, vomiting
Valproate	40 mg/kg IV (max infusion rate 10 mg/kg/min) Maintenance: 10-60 mg/kg/d in divided doses	Hepatotoxicity, pancreatitis, thrombocytopenia, hyperammonemia, rash	Somnolence, diplopia nausea, vomiting, diarrhea
Intracranial Pressure Elevation			

Drug	Dosing	Rare Toxicities	Common Toxicities
Hypertonic saline	NaCl 5%: 3-4 mL/kg IV NaCl 23.4%: 15-60 mL IV (central line required)	Phlebitis	Hypernatremia, hyperchloremia
Mannitol	1-1.5 g/kg IV bolus, then 0.25-1 g/kg as needed	—	Hypotension, acute renal failure, fluid and electrolyte imbalances
Stroke			
Alteplase	Ischemic stroke: 0.9 mg/kg IV (max 90 mg), infused over 60 min with 10% of the dose given as an initial bolus over 1 min	—	Bleeding
Tenecteplase	0.25 mg/kg IV (max 25 mg) bolus × 1	—	Bleeding
ICU Delirium			
Haloperidol	2.5-10 mg IV/IM PRN	QTc prolongation, extrapyramidal side effects (dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia), neuroleptic malignant syndrome	CNS depression, orthostatic hypotension
ICU Sedation			
Fentanyl	0-400 mcg/h	Hypotension	Constipation, respiratory depression, CNS depression

Drug	Dosing	Rare Toxicities	Common Toxicities
Propofol	10-50 mcg/kg/min	Pancreatitis, propofol infusion syndrome	Hypotension, bradycardia, CNS depression, hypertriglyceridemia
Dexmedetomidine	0.2-1.5 mcg/kg/h	—	Hypotension, bradycardia
Ketamine	0-200 mg/h	Increased intracranial and intraocular pressure, laryngospasm	Increased heart rate and blood pressure, emergence reactions
Midazolam	1-12 mg/h	Paradoxical excitation, hypotension	CNS depression, respiratory depression
Rapid Sequence Intubation			
Etomidate	0.3 mg/kg IV × 1	Adrenal insufficiency	
Ketamine	1-2 mg/kg	Increased intracranial and intraocular pressure, laryngospasm	Increased heart rate and blood pressure, emergency reactions
Midazolam	0.5-0.1 mg/kg IV × 1	Paradoxical excitation, hypotension, respiratory depression (high doses)	CNS depression
Propofol	1 mg/kg IV × 1	Pancreatitis, propofol infusion syndrome	Hypotension, bradycardia, CNS depression, hypertriglyceridemia
Succinylcholine	1-2 mg/kg IV × 1	Malignant hyperthermia, bradycardia, increased intracranial and intraocular pressure	Hyperkalemia
Rocuronium	0.6-1.2 mg/kg IV × 1	Residual muscle weakness	

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

CNS, central nervous system; ICU, intensive care unit; IM, intramuscular; IV, intravenous; PO, by mouth; NaCl, sodium chloride.

TABLE 95.13 Hyper- and Hypocoagulability Disorders

Drug	Dosing	Rare Toxicities	Common Toxicities
Oral Anticoagulants			
Warfarin	Initial 1-5 mg/d, adjust based on INR measurements	Skin necrosis, purple-toe syndrome	Bleeding
Apixaban	10 mg PO BID × 7 d (only for DVT/PE), then 5 mg PO BID		Bleeding
Rivaroxaban	15 mg PO BID with food × 21 d (only for DVT/PE), then 20 mg PO daily with evening meal		Bleeding
Reversal Agents			
Phytonadione (vitamin K)	1-10 mg IV/PO Q24H	IV form: anaphylaxis, hypotension	—
4-Factor prothrombin complex concentrate (Kcentra)	25-50 U/kg IV × 1	Hypotension, thrombosis	Headache
Andexxa	Low dose: 400 mg IV bolus, then IV infusion of 4 mg/min for up to 120 min High dose: 800 mg IV bolus, then IV infusion of 8 mg/min for up to 120 min	Thromboembolic and ischemic events, infusion reactions, antibody development	
Other Agents			
Desmopressin (DDAVP)	0.3-0.4 mcg/kg IV × 1	Hyponatremia, hypotension, tachycardia, thrombosis	Facial flushing

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

BID, twice daily; DVT, deep vein thrombosis; INR, international normalized ratio; IV, intravenous; PE, pulmonary embolism; PO, by mouth; U, units.

TABLE 95.14 Pregnancy

Drug	Dosing	Rare Toxicities	Common Toxicities
Magnesium	4-6 g IV over 15-20 min, then 2 g/h infusion	—	
Oxytocin	1-2 mL/h, titrate up to 20-40 mL/h to desired contraction pattern	—	Uterine tachysystole
Labetalol	100-800 mg PO Q8-12H	Heart block, bronchoconstriction	Hypotension, bradycardia, nausea, vomiting
Hydralazine	10-40 mg IV Q4-6H or 10-75 mg PO TID-QID	Drug-induced lupus-like syndrome, rash, peripheral neuropathy	Hypotension, tachycardia, flushing, headache

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

IV, intravenous; PO, by mouth; QID, four times a day; TID, three times a day.